HALOZYME THERAPEUTICS INC
Form 10-K
February 21, 2019

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 10-K
x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018
OR
¨ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to
Commission File Number 001-32335

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HALOZYME THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

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Delaware	88-0488686
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
11388 Sorrento Valley Road, San Diego, CA	92121
(Address of principal executive offices)	(Zip Code)

(858) 794-8889
(Registrant's telephone number, including area code)
Securities registered under Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.001 Par Value	The NASDAQ Stock Market, LLC

Securities registered under Section 12(g) of the Act:
None
Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. x Yes ¨ No
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. ¨ Yes x No
Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. x Yes ¨ No
Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). x Yes ¨ No
Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or emerging growth company. See the definitions of “large accelerated filer,” “accelerated filer”, “smaller reporting company” and “emerging growth company” in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer	Non-accelerated filer	Smaller reporting company	Emerging growth company
x	¨	¨	¨	¨

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). ¨ Yes x No

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2018 was approximately $2.1 billion based on the closing price on the NASDAQ Global Select Market reported for such date. Shares of common stock held by each officer and director and by each person who is known to own 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates of the registrant. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of outstanding shares of the registrant’s common stock, par value $0.001 per share, was 145,033,173 as of February 14, 2019.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant’s definitive Proxy Statement to be filed subsequent to the date hereof with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant’s 2019 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report.

HALOZYME THERAPEUTICS, INC.
INDEX

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of the "safe harbor" provisions of Section 21E of the Securities Exchange Act of 1934, as amended, and Section 27A of the Securities Act of 1933, as amended. All statements, other than statements of historical fact, included herein, including without limitation those regarding our future product development and regulatory events and goals, product collaborations, our business intentions and financial estimates and anticipated results, are forward-looking statements. Words such as "expect," "anticipate," "intend," "plan," "believe," "seek," "estimate," "think," "may," "could," "will," "would," "should," "co "likely," "opportunity" and similar expressions or variations of such words are intended to identify forward-looking statements, but are not the exclusive means of identifying forward-looking statements in this Annual Report. Additionally, statements concerning future matters such as the development or regulatory approval of new products, enhancements of existing products or technologies, third party performance under key collaboration agreements, revenue and expense levels and other statements regarding matters that are not historical are forward-looking statements.

Although forward-looking statements in this Annual Report reflect the good faith judgment of our management, such statements can only be based on facts and factors currently known by us. Consequently, forward-looking statements are inherently subject to risks and uncertainties and actual results and outcomes may differ materially from the results and outcomes discussed in or anticipated by the forward-looking statements. Factors that could cause or contribute to such differences in results and outcomes include without limitation those discussed under the heading "Risk Factors" in Part I, Item 1A below, as well as those discussed elsewhere in this Annual Report. Readers are urged not to place undue reliance on these forward-looking statements, which speak only as of the date of this Annual Report. We undertake no obligation to revise or update any forward-looking statements in order to reflect any event or circumstance that may arise after the date of this Annual Report. Readers are urged to carefully review and consider the various disclosures made in this Annual Report, which attempt to advise interested parties of the risks and factors that may affect our business, financial condition, results of operations and prospects.

References to "Halozyme," "the Company," "we," "us," and "our" refer to Halozyme Therapeutics, Inc. and its wholly owned subsidiary, Halozyme, Inc., and Halozyme, Inc.'s wholly owned subsidiaries, Halozyme Holdings Ltd., Halozyme Royalty LLC, Halozyme Switzerland GmbH and Halozyme Switzerland Holdings GmbH. References to "Notes" refer to the Notes to Consolidated Financial Statements included herein (refer to Part II, Item 8).

PART I

Item 1. Business

Overview

Halozyme Therapeutics, Inc. is a biotechnology company focused on developing and commercializing novel oncology therapies. We are seeking to translate our unique knowledge of the tumor microenvironment to create therapies that have the potential to improve cancer patient survival. Our research primarily focuses on human enzymes that alter the extracellular matrix and tumor microenvironment. The extracellular matrix is a complex matrix of proteins and carbohydrates surrounding the cell that provides structural support in tissues and orchestrates many important biological activities, including cell migration, signaling and survival. Over many years, we have developed unique technology and scientific expertise enabling us to pursue this target-rich environment for the development of therapies.

Our proprietary enzymes are used to facilitate the delivery of injected drugs and fluids, potentially enhancing the efficacy and the convenience of other drugs or can be used to alter tissue structures for potential clinical benefit. We exploit our technology and expertise using a two pillar strategy that we believe enables us to manage risk and cost by: (1) developing our own proprietary products in therapeutic areas with significant unmet medical needs, with a focus on oncology, and (2) licensing our technology to biopharmaceutical companies to collaboratively develop products that combine our technology with the collaborators' proprietary compounds.

The majority of our approved product and product candidates are based on rHuPH20, our patented recombinant human hyaluronidase enzyme. rHuPH20 is the active ingredient in our first commercially approved product, Hylenex® recombinant, and it works by temporarily breaking down hyaluronan (or HA), a naturally occurring carbohydrate that is a major component of the extracellular matrix in tissues throughout the body such as skin and cartilage. We believe this temporary degradation creates an opportunistic window for the improved subcutaneous delivery of injectable biologics, such as monoclonal antibodies and other large therapeutic molecules, as well as small molecules and fluids. We refer to the application of rHuPH20 to facilitate the delivery of other drugs or fluids as our ENHANZE® Drug Delivery Technology (ENHANZE). We license the ENHANZE technology to form collaborations with biopharmaceutical companies that develop or market drugs requiring or benefiting from injection via the subcutaneous route of administration.

We currently have ENHANZE collaborations with F. Hoffmann-La Roche, Ltd. and Hoffmann-La Roche, Inc. (Roche), Baxalta US Inc. and Baxalta GmbH (now members of the Takeda group of companies, following the acquisition of Shire plc by Takeda Pharmaceutical Company Limited in January 2019) (Baxalta), Pfizer Inc. (Pfizer), Janssen Biotech, Inc. (Janssen), AbbVie, Inc. (AbbVie), Eli Lilly and Company (Lilly), Bristol-Myers Squibb Company (BMS), Alexion Pharma Holding (Alexion) and ARGENX BVBA (argenx). We receive royalties from two of these collaborations, including royalties from sales of one product from the Baxalta collaboration and two products from the Roche collaboration. Future potential revenues from the sales and/or royalties of our approved products, product candidates, and ENHANZE collaborations will depend on the ability of Halozyme and our collaborators to develop, manufacture, secure and maintain regulatory approvals for approved products and product candidates and commercialize product candidates.

Our proprietary development pipeline consists primarily of pre-clinical and clinical stage product candidates in oncology. Our lead oncology program is Pegvorhyaluronidase alfa (PVHA), also referred to as PEGylated recombinant human hyaluronidase (PEGPH20), a molecular entity we are developing in combination with currently approved cancer therapies as a candidate for the systemic treatment of tumors that accumulate HA. We have demonstrated that when HA accumulates in a tumor, it can cause increased pressure in the tumor, reducing blood flow into the tumor and with that, reduced access of cancer therapies to the tumor. PEGPH20 has been demonstrated in animal models to work by temporarily degrading HA surrounding cancer cells resulting in reduced pressure and increased blood flow to the tumor thereby enabling increased amounts of anticancer treatments administered concomitantly gaining access to the tumor. Through our efforts and efforts of our partners and collaborators, we are currently in Phase 3 clinical testing for PEGPH20 with ABRAXANE® (nab-paclitaxel) and gemcitabine in stage IV pancreatic ductal adenocarcinoma (PDA) (HALO 109-301), in Phase 1b clinical testing for PEGPH20 with KEYTRUDA® (pembrolizumab) in non-small cell lung cancer (HALO 107-101), in Phase 1b/2 clinical testing for PEGPH20 with Tecentriq® (atezolizumab) in patients with previously treated metastatic PDA, in Phase 1b/2 clinical testing for PEGPH20 with Tecentriq in patients with gastric cancer and in Phase 1b/2 clinical testing for PEGPH20 with Tecentriq in patients with cholangiocarcinoma and gall bladder cancer (HALO 110-101/MATRIX).

Our principal offices and research facilities are located at 11388 Sorrento Valley Road, San Diego, California 92121. Our telephone number is (858) 794-8889 and our e-mail address is info@halozyme.com. Our website address is www.halozyme.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K. Our periodic and current reports that we filed with the SEC are available on our website at www.halozyme.com, free of charge, as soon as reasonably practicable after we have electronically filed such material with, or furnished them to, the SEC, including our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and any amendments to those reports.

Technology

rHuPH20 can be applied as a drug delivery platform to increase dispersion and absorption of other injected drugs and fluids that are injected under the skin or in the muscle thereby potentially enhancing efficacy or convenience. For example, rHuPH20 has been used to convert drugs that must be delivered intravenously into subcutaneous injections or to reduce the number of subcutaneous injections needed for effective therapy. When ENHANZE Technology is applied subcutaneously, the rHuPH20 acts locally and has a tissue half-life of less than 15 minutes. HA at the local site reconstitutes its normal density within a few days and, therefore, we anticipate that any effect of rHuPH20 on the

architecture of the subcutaneous space is temporary.

Additionally, we are expanding our scientific work to develop other enzymes and agents that target the extracellular matrix's unique aspects, giving rise to potentially new molecular entities with a particular focus on oncology. We are developing a PEGylated version of the rHuPH20 enzyme (PEGPH20), that lasts for an extended period in the bloodstream (half-life of one to two days), and may therefore better target solid tumors that accumulate HA by degrading the surrounding HA and reducing the interstitial fluid pressure within malignant tumors to allow better penetration by co-administered agents.

Strategy

During 2018, we continued our strategy of focusing on developing our oncology pipeline and expanding our collaborations for ENHANZE Technology. This business model allows for revenue garnered from collaboration products to help fund our investment in PEGPH20 clinical development, with the goal of a future product approval that will support sustained growth.

Key aspects of our corporate strategy include the following:

- Focus on our oncology pipeline. We are currently developing PEGPH20, our investigational new drug candidate, in multiple different tumors that accumulate high levels of HA. PEGPH20 is in Phase 3 development in stage IV PDA and multiple Phase 1b/2 studies for various tumor types. Over time, it is our goal to study additional types of cancer and to advance this program toward regulatory approval and commercial launch. In addition, we have a novel oncology preclinical asset.
- Focus on our ENHANZE platform. We currently have nine collaborations with three current product approvals and additional product candidates in development. We intend to work with our existing collaborators to expand our collaborations to add new targets and develop targets and product candidates under the terms of the operative agreements. In addition, we will continue our efforts to enter into new collaborations to further derive additional value from our proprietary technology.

Product and Product Candidates

We have one marketed proprietary product, three partnered products, one proprietary product candidate targeting several indications in various stages of development, and one preclinical product candidate. The following table summarizes our proprietary product and product candidate as well as products and product candidates under development with our collaborators:

Proprietary Pipeline

Hylenex Recombinant (hyaluronidase human injection)

Hylenex recombinant is a formulation of rHuPH20 that has received U.S. Food and Drug Administration (FDA) approval to facilitate subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs and, in subcutaneous urography, to improve resorption of radiopaque agents. Hylenex recombinant is currently the number one prescribed branded hyaluronidase.

PEGPH20

We are developing PEGPH20 in combination with currently approved cancer therapies as a candidate for the systemic treatment of tumors that accumulate HA. ‘PEG’ refers to the attachment of polyethylene glycol to rHuPH20, thereby creating PEGPH20. One of the novel properties of PEGPH20 is that it lasts for an extended duration in the bloodstream and, therefore, can be administered systemically to maintain its therapeutic effect to treat disease. Cancer malignancies, including pancreatic, lung, breast, gastric, and biliary tract cancers can accumulate high levels of HA and therefore we believe that PEGPH20 has the potential to help patients with these types of cancer when used with certain currently approved cancer therapies. Among solid tumors, PDA has been reported to be associated with one of the highest frequencies of HA accumulation. There are approximately 65,000 annual diagnoses of PDA in the United States and the European Union, and we estimate that 35-40% have high levels of HA based on our companion diagnostic assay cutpoint.

The pathologic accumulation of HA, along with other matrix components, creates a unique microenvironment for the growth of tumor cells compared to normal cells. We believe that degrading the HA component of the tumor microenvironment with PEGPH20 remodels the tumor microenvironment, resulting in tumor growth inhibition in animal models. Removal of HA from the tumor microenvironment results in expansion of previously constricted blood vessels allowing increased blood flow, potentially increasing the access of activated immune cells and factors in the blood into the tumor microenvironment. If PEGPH20 is administered in conjunction with other anti-cancer therapies, the increase in blood flow may allow anti-cancer therapies to have greater access to the tumor, which may enhance the treatment effect of therapeutic modalities like chemotherapies, monoclonal antibodies and other agents. We are developing PEGPH20 as a targeted therapy, for patients who have tumors with high levels of HA. We have a collaboration with Ventana Medical Systems Inc. (Ventana), a member of the Roche Group, to develop, and for Ventana to ultimately commercialize, a companion diagnostic assay for use with PEGPH20. The companion diagnostic assay is being used to identify high levels of HA in tumor biopsies, and may be the first diagnostic to target tumor-associated HA and possibly the first companion diagnostic assay in pancreatic cancer.

Pancreatic cancer indications:

Based on the results of Phase 1b and Phase 2 studies, HALO 109-201 and HALO 109-202, we embarked on a double blinded, placebo controlled study in previously untreated pancreas cancer patients to test PEGPH20 plus gemcitabine and nab-paclitaxel (ABRAXANE®) versus gemcitabine and ABRAXANE alone.

HALO 109-301:

In March 2015, we met with the FDA to discuss the interim efficacy and safety data from HALO-202, and the proposed selection of eligible patients based on a 50% cutpoint using the Ventana companion diagnostic. Based on the feedback from that meeting, we proceeded with HALO 109-301 (HALO-301), a Phase 3 multicenter randomized clinical trial evaluating PEGPH20 as a first-line therapy for patients with stage IV PDA, using a design allowing for potential marketing application based on PFS (accelerated approval pathway) or OS. The study enrolled patients whose tumors accumulate high levels of HA measured using the Ventana companion diagnostic test. The FDA provided feedback on the current companion diagnostic approach and confirmed that an approved investigational device exemption (IDE) was required for the Phase 3 study.

In June 2015, we received scientific advice/protocol assistance from the European Medicines Agency (EMA) regarding our Phase 3 study. The EMA agreed to the patient population, and the use of both PFS and OS as co-primary endpoints stating that OS is the preferred endpoint and that ultimate approval would require an overall positive benefit:risk balance.

In March 2016, Ventana received approval for an IDE application from the FDA for our companion diagnostic test to enable patient selection in our Phase 3 Study HALO-301 of PEGPH20 in HA-High patients and we dosed the first patient in HALO-301. In January 2019, our independent Data Safety Monitoring Committee met to review ongoing safety data from the trial and informed us the study should proceed as planned.

In November 2018, the FDA agreed to our request to change the primary endpoint of the HALO-301 study from two primary endpoints of PFS and OS to a single primary endpoint of OS. As a result, a previously planned interim analysis, that was to be performed when the target number of PFS events was achieved, will not be conducted. PFS will remain as a secondary endpoint, along with objective response rate. In January 2019, the FDA completed their review of the submitted clinical study protocol amendment and statistical analysis plan with no additional questions or comments. Over 200 sites in 22 countries located in North America, Europe, South America and Asia were initiated to participate in the HALO-301 study. The study was fully enrolled with approximately 500 patients by the end of 2018. We project that the target number of 330 OS events for the final analysis will be achieved between August and November 2019.

SWOG Study S1313:

In October 2013, SWOG, a cancer research cooperative group of more than 4,000 researchers in over 500 institutions around the world, initiated a 144 patient Phase 1b/2 randomized clinical trial in some of their study centers, examining PEGPH20 in combination with modified FOLFIRINOX chemotherapy compared to modified FOLFIRINOX treatment alone in patients with stage IV PDA, irrespective of HA levels, referred to as an all-comer population. This study was funded by the National Cancer

6

Institute. In March 2017, SWOG stopped enrollment in the Phase 1b/2 trial following a recommendation of SWOG's independent Data Monitoring committee after a preplanned futility analysis. In January 2018, SWOG presented final data of the all-comers population at the ASCO-GI conference. The median overall survival was 7.7 months for the PEGPH20 arm vs. 14.4 months in the modified FOLFIRINOX alone arm. Also, increased GI-toxicities and substantially shorter median treatment duration for modified FOLFIRINOX were reported for the PEGPH20 arm compared to the modified FOLFIRINOX alone arm. Collection of biopsy samples from participating sites to potentially enable an HA biomarker subgroup analysis has been completed. Due to the limited number of samples available, it is not known if the data will be interpretable. Our PEGPH20 studies and clinical collaborations in combination with agents other than modified FOLFIRINOX continue unchanged.

Clinical collaboration:

In October 2016, we announced that PEGPH20 will be included in a pancreatic cancer clinical trial initiative called Precision Promise, an initiative that aims to change the current treatment approach to pancreatic cancer by offering options to patients based on the molecular profile of their tumor. This is being accomplished through the Pancreatic Cancer Action Network leading a collaboration that brings together clinicians, researchers, and drug developers. Pancreatic Cancer Action Network continues to work to finalize the trial design and protocol which may include a potential PEGPH20 trial arm or trial.

Other indications outside of pancreatic cancer:

HALO 107-101:

In November 2015, we initiated a Phase 1b study exploring the combination of PEGPH20 and KEYTRUDA®, an immuno-oncology agent in relapsed non-small cell lung cancer (NSCLC) and gastric cancer. In December 2016, we identified a dose of PEGPH20, namely 2.2 ug/kg, to move into the dose expansion phase of the study with KEYTRUDA in combination with PEGPH20. In September 2017, our standing Independent Data Monitoring Safety Committee met to review ongoing safety data from the trial and informed us that the study should proceed with study protocol modifications to exclude patients at risk and increase liver safety monitoring, after observing clinical and laboratory signs of hepato-biliary dysfunction. In April 2018, we informed participating sites to stop screening for new patients in the gastric cancer cohort of the study as the overall enrollment goal has been reached. Patients already in screening prior to the notification date were allowed to enter the study contingent of all eligibility criteria being met. Following the results of Merck's KEYNOTE-189 study evaluating KEYTRUDA in combination with chemotherapy as a first-line treatment, the standard of care in lung cancer is expected to change. As we are seeking to enroll second line immune checkpoint inhibitor naïve patients, we have closed enrollment in the lung cohort of the study and investigators were given the option to continue treatment of ongoing patients.

HALO 107-101 is an ongoing study with an open database and enrollment has ended in both the NSCLC and gastric cancer cohorts. In the NSCLC cohort we enrolled 17 of the target 30 patients in the dose expansion cohort prior to closing enrollment. One patient is ongoing. Of the 13 currently evaluable patients, four patients experienced a greater than 30% reduction in tumor volume as assessed by investigator sites. Two of these patients had a further scan confirming the greater than 30% reduction was maintained. Of the four patients experiencing a greater than 30% reduction, three were PD-L1 negative, while data was unavailable for the fourth. Discussions are ongoing with advisers and investigators regarding the data and any next steps.

In the gastric cancer cohort, we reached target enrollment of 34 patients in the dose finding and dose expansion cohort. Of the 26 currently evaluable patients, we have seen one responder in a PD-L1 positive patient. This response rate does not meet our threshold to continue development of PEGPH20 in combination with Keytruda alone in gastric cancer.

We continue to collect and receive data on both NSCLC and gastric patients. When the database is considered complete and locked, a Final Study Report will be generated and data presented.

Ongoing clinical collaboration:

In November 2016, we entered into an agreement with Genentech, a member of the Roche Group, to collaborate on clinical studies to evaluate their cancer immunotherapy Tecentriq, an anti-PD-L1 monoclonal antibody, in combination with PEGPH20, in up to eight different tumor types. Genentech initiated a Phase 1b/2 clinical trial in patients with previously treated metastatic PDA in July 2017 and a Phase 1b/2 clinical trial in patients with gastric cancer in October 2017, as part of its Morpheus master protocol. In February 2019, Genentech closed enrollment in the gastric arm of the study and results will be reported when data is available. We will supply PEGPH20 for the Genentech-funded studies. In October 2017, we initiated a Phase 1b/2 clinical trial to assess Tecentriq with PEGPH20 in patients with cholangiocarcinoma and gall bladder cancer (HALO 110-101/MATRIX). Genentech will supply Tecentriq for the Halozyme sponsored study.

Regulatory

The FDA has granted Fast Track designation for our program investigating PEGPH20 in combination with gemcitabine and nab-paclitaxel for the treatment of patients with stage IV PDA to demonstrate an improvement in OS. The Fast Track designation process was developed by the FDA to facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases and address unmet medical needs.

The FDA has granted Orphan Drug designation for PEGPH20 for the treatment of pancreatic cancer. The FDA Office of Orphan Products Development's mission is to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. Similarly, the European Committee for Orphan Medicinal Products of the EMA designated PEGPH20 an orphan medicinal product for the treatment of pancreatic cancer.

Other Pipeline Asset

PEG-ADA2: PEGylated adenosine deaminase 2, or PEG-ADA2, is an immune checkpoint inhibitor that targets adenosine, which may accumulate to high levels in the tumor microenvironment and has been linked to immunosuppression. We are currently in preclinical development with PEG-ADA2 and are exploring potential collaboration or partnership interest in this program prior to making additional investments in the development of PEG-ADA2.

ENHANZE Collaborations

Roche Collaboration

In December 2006, we and Roche entered into a collaboration and license agreement under which Roche obtained a worldwide license to develop and commercialize product combinations of rHuPH20 and up to thirteen Roche target compounds (the Roche Collaboration). Under this agreement, Roche elected a total of eight targets, two of which are exclusive.

In September 2013, Roche launched a subcutaneous (SC) formulation of Herceptin (trastuzumab) (Herceptin SC) in Europe for the treatment of patients with HER2-positive breast cancer followed by launches in additional countries. This formulation utilizes our ENHANZE technology and is administered in two to five minutes, compared to 30 to 90 minutes with the standard intravenous form. Directed at the same target, Roche initiated a Phase 1 study of PERJETA® (pertuzumab) and Herceptin (trastuzumab) with ENHANZE in patients with early breast cancer in March 2016. In June 2018, Roche initiated a global Phase 3 study of a fixed-dose combination of PERJETA and Herceptin with ENHANZE in patients with HER2-positive early breast cancer. In July 2018, we announced the FDA accepted a BLA from Genentech (a member of the Roche Group) for Herceptin SC in its FDA-approved breast cancer indications. Approval of the BLA is expected in March 2019. In September 2018, we announced that Roche received approval from Health Canada for Herceptin SC for the treatment of patients with HER2-positive breast cancer.

In June 2014, Roche launched MabThera SC in Europe for the treatment of patients with common forms of non-Hodgkin lymphoma (NHL) followed by launches in additional countries. This formulation utilizes our ENHANZE technology and is administered in approximately five minutes compared to the approximately 1.5 to 4 hour intravenous infusion. In May 2016, Roche announced that the EMA approved Mabthera SC to treat patients with chronic lymphocytic leukemia (CLL). In June 2017, the FDA approved Genentech's RITUXAN HYCELA™, a combination of rituximab and rHuPH20 (approved and marketed under

8

the MabThera SC brand in countries outside the U.S.), for CLL and two types of NHL, follicular lymphoma and diffuse large B-cell lymphoma.

In September 2017, we and Roche entered into an agreement providing Roche the right to develop and commercialize one additional exclusive target using our ENHANZE technology. The upfront license payment may be followed by event-based payments subject to Roche's achievement of specified development, regulatory and sales-based milestones. In addition, Roche will pay royalties to us if products under the collaboration are commercialized.

In January 2018, Roche initiated a Phase 1 study of an undisclosed target with ENHANZE technology. In February 2019, Roche canceled development of the undisclosed target following discontinuation of the proprietary program.

In October 2018, we entered into an agreement with Roche for the right to develop and commercialize one additional exclusive target and an option to select two additional targets within four years using our ENHANZE technology. The upfront license payment may be followed by event-based payments subject to Roche's achievement of specified development, regulatory and sales-based milestones. In addition, Roche will pay royalties to us if products under the collaboration are commercialized.

In December 2018, Roche initiated a Phase 1b/2 study in patients with non-small cell lung cancer for Tecentriq (atezolizumab) in combination with our ENHANZE technology.

Baxalta Collaboration

In September 2007, we and Baxalta entered into a collaboration and license agreement under which Baxalta obtained a worldwide, exclusive license to develop and commercialize product combinations of rHuPH20 with GAMMAGARD LIQUID (HYQVIA) (the Baxalta Collaboration). HYQVIA is indicated for the treatment of primary immunodeficiency disorders associated with defects in the immune system.

In May 2013, the European Commission granted Baxalta marketing authorization in all EU Member States for the use of HYQVIA (solution for subcutaneous use) as replacement therapy for adult patients with primary and secondary immunodeficiencies. Baxalta launched HYQVIA in the first EU country in July 2013 and has continued to launch in additional countries.

In September 2014, HYQVIA was approved by the FDA for treatment of adult patients with primary immunodeficiency in the U.S. HYQVIA is the first subcutaneous immune globulin (IG) treatment approved for adult primary immunodeficiency patients with a dosing regimen requiring only one infusion up to once per month (every three to four weeks) and one injection site per infusion in most patients, to deliver a full therapeutic dose of IG. The FDA's approval of HYQVIA was a significant milestone for us as it represented the first U.S. approved BLA which utilizes our rHuPH20 platform.

In May 2016, Baxalta announced that HYQVIA received a marketing authorization from the European Commission for a pediatric indication, which was launched in Europe to treat primary and certain secondary immunodeficiencies.

Pfizer Collaboration

In December 2012, we and Pfizer entered into a collaboration and license agreement, under which Pfizer has the worldwide license to develop and commercialize products combining our rHuPH20 enzyme with Pfizer proprietary biologics directed to up to six targets in primary care and specialty care indications. Targets may be selected on an exclusive or non-exclusive basis. Pfizer has elected five targets on an exclusive basis and returned two targets.

Janssen Collaboration

In December 2014, we and Janssen entered into a collaboration and license agreement, under which Janssen has the worldwide license to develop and commercialize products combining our rHuPH20 enzyme with Janssen proprietary biologics directed to up to five targets. Targets may be selected on an exclusive basis. Janssen has elected CD38 as the first target on an exclusive basis. In October 2017, Janssen initiated its first Phase 3 study of subcutaneous delivery of DARZALEX® (daratumumab), directed at CD38, using ENHANZE technology, in multiple myeloma patients. Janssen has initiated six Phase 3 studies, one Phase 2 study and one Phase 1 study of daratumumab combined with the ENHANZE technology in patients with amyloidosis, smoldering myeloma and multiple myeloma.

AbbVie Collaboration

In June 2015, we and AbbVie entered into a collaboration and license agreement, under which AbbVie has the worldwide license to develop and commercialize products combining our rHuPH20 enzyme with AbbVie proprietary biologics directed to up to nine targets. Targets may be selected on an exclusive basis. AbbVie elected one target on an exclusive basis, TNF alpha, for which it has discontinued development and returned the target.

Lilly Collaboration

In December 2015, we and Lilly entered into a collaboration and license agreement, under which Lilly has the worldwide license to develop and commercialize products combining our rHuPH20 enzyme with Lilly proprietary biologics directed to up to five targets. Targets may be selected on an exclusive basis. Lilly has elected two targets on an exclusive basis and one target on a semi-exclusive basis. In August 2017, Lilly initiated a Phase 1 study of an investigational new therapy in combination with rHuPH20.

BMS Collaboration

In September 2017, we and BMS entered into a collaboration and license agreement, which became effective in November 2017, under which BMS has the worldwide license to develop and commercialize products combining our rHuPH20 enzyme with BMS immuno-oncology targets directed at up to eleven targets. Targets may be selected on an exclusive basis, with the exception of one co-exclusive target. BMS has designated multiple immuno-oncology targets including programmed death 1 (PD-1) and has an option to select additional targets within five years from the effective date. In October 2018, BMS dosed the first patient in a Phase 1 study evaluating the safety, pharmacokinetics and pharmacodynamics of BMS-986179, an investigational anti-CD-73 antibody and ENHANZE technology. BMS is currently in a Phase 1 study of OPDIVO® (nivolumab) with ENHANZE.

Alexion Collaboration

In December 2017, we and Alexion entered into a collaboration and license agreement, under which Alexion has the worldwide license to develop and commercialize products combining our rHuPH20 enzyme with Alexion’s portfolio of products directed at up to four targets. Targets may be selected on an exclusive basis. Alexion elected two targets on an exclusive basis, including a C5 complement inhibitor and has an option to select two additional targets within five years from the effective date. In August 2018, Alexion initiated a Phase 1 trial to study a next-generation subcutaneous formulation of ALXN1210 with ENHANZE technology.

argenx Collaboration

In February 2019, we entered into an agreement with argenx for the right to develop and commercialize one exclusive target, the human neonatal Fc receptor FcRn, which includes argenx's lead asset efgartigimod (ARGX-113), and an option to select two additional targets using our ENHANZE technology.

For a further discussion of the collaboration agreements, refer to Note 2, Summary of Significant Accounting Policies - Revenues under Collaborative Agreements.

Customers

The following table indicates the percentage of total revenues in excess of 10% with any single customer:

	Year Ended December 31,		
	2018	2017	2016
Roche	72%	38%	63%
Baxalta	7 %	7 %	12%
BMS	4 %	32%	—
Alexion	3 %	13%	—

For additional information regarding our revenues from customers, refer to Note 2, Summary of Significant Accounting Policies — Concentrations of Credit Risk, Sources of Supply and Significant Customers, to our consolidated financial statements.

Patents and Proprietary Rights

Patents and other proprietary rights are essential to our business. Our success will depend in part on our ability to obtain patent protection for our inventions, to preserve our trade secrets and to operate without infringing the proprietary rights of third parties. Our strategy is to actively pursue patent protection in the U.S. and certain foreign jurisdictions for technology that we believe to be proprietary to us and that offers us a potential competitive advantage. Our patent portfolio includes 39 issued patents in the U.S., more than 390 issued patents in Europe and other countries in the world and more than 100 pending patent applications. In general, patents have a term of 20 years from the application filing date or earlier claimed priority date. Our issued patents will expire between 2022 and 2033.

We have multiple patents and patent applications throughout the world pertaining to our recombinant human hyaluronidase and methods of use and manufacture, including an issued U.S. patent which expires in 2027 and an issued European patent which expires in 2024, which we believe cover the products and product candidates under our existing collaborations, Hylenex recombinant and PEGPH20. In addition, we have, under prosecution throughout the world, multiple patent applications that relate specifically to individual product candidates under development, the expiration of which can only be definitely determined upon maturation into our issued patents. We believe our patent filings represent a barrier to entry for potential competitors looking to utilize these hyaluronidases.

In addition to patents, we rely on unpatented trade secrets, proprietary know-how and continuing technological innovation. We seek protection of these trade secrets, proprietary know-how and innovation, in part, through confidentiality and proprietary information agreements. Our policy is to require our employees, directors, consultants, advisors, collaborators, outside scientific collaborators and sponsored researchers, other advisors and other individuals and entities to execute confidentiality agreements upon the start of employment, consulting or other contractual relationships with us. These agreements provide that all confidential information developed or made known to the individual or entity during the course of the relationship is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees and some other parties, the agreements provide that all inventions conceived by the individual will be our exclusive property. Despite the use of these agreements and our efforts to protect our intellectual property, there will always be a risk of unauthorized use or disclosure of information. Furthermore, our trade secrets may otherwise become known to, or be independently developed by, our competitors.

We also file trademark applications to protect the names of our products and product candidates. These applications may not mature to registration and may be challenged by third parties. We are pursuing trademark protection in a number of different countries around the world. There can be no assurances that our registered or unregistered trademarks or trade names will not infringe on rights of third parties or will be acceptable to regulatory agencies.

Research and Development Activities

Our research and development expenses consist primarily of costs associated with the development and manufacturing of our product candidates, compensation and other expenses for research and development personnel, supplies and materials, costs for consultants and related contract research, clinical trials, facility costs and amortization and depreciation. We charge all research and development expenses to operations as they are incurred. Our research and development activities are primarily focused on the development of our various product candidates.

Due to the uncertainty in obtaining the FDA and other regulatory approvals, our reliance on third parties and competitive pressures, we are unable to estimate with any certainty the additional costs we will incur in the continued development of our proprietary product candidates for commercialization. However, we expect our research and development expenses for PEGPH20 to increase as our program advances into additional tumors and later stages of clinical development.

Manufacturing

We do not have our own manufacturing facility for our product and product candidates, or the capability to package our products. We have engaged third parties to manufacture bulk rHuPH20, PEGPH20 and Hylenex recombinant.

We have existing supply agreements with contract manufacturing organizations Avid Bioservices, Inc. (Avid) and Catalent Indiana LLC (formerly Cook Pharmica LLC) (Catalent) to produce supplies of bulk rHuPH20. These manufacturers each produce bulk rHuPH20 under current Good Manufacturing Practices (cGMP) for clinical and commercial uses. Catalent currently produces bulk rHuPH20 for use in Hylenex recombinant, product candidates and collaboration product candidates. Avid currently pro