

ARROWHEAD RESEARCH CORP  
Form 10-K  
December 14, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

(Mark One)

ANNUAL REPORT UNDER SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934  
For the fiscal year ended September 30, 2015.

TRANSITION REPORT UNDER SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934  
For the transition period from \_\_\_\_\_ to \_\_\_\_\_

Commission file number 000-21898

ARROWHEAD RESEARCH CORPORATION

(Exact name of registrant as specified in its charter)

Delaware 46-0408024  
(State of incorporation) (I.R.S. Employer Identification No.)  
225 S. Lake Avenue, Suite 1050

Pasadena, California 91101

(626) 304-3400

(Address and telephone number of principal executive offices)

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Securities registered under Section 12(b) of the Exchange Act:

Title of each class	Name of each exchange on which registered
Common Stock, \$0.001 par value	The NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Exchange Act:

None

Indicate by a check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes  No

Indicate by a check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes  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. Yes  No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes  No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K 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.

Indicate by check mark whether the Registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act.

Large accelerated filer  Accelerated filer  Non-accelerated filer  Smaller Reporting Company   
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes  No

The aggregate market value of issuer's voting and non-voting outstanding Common Stock held by non-affiliates was approximately \$407 million based upon the closing stock price of issuer's Common Stock on March 31, 2015. 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 Company. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of December 11, 2015, 59,554,677 shares of the issuer's Common Stock were issued and outstanding.

#### DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Definitive Proxy Statement to be filed for Arrowhead Research Corporation's 2016 Annual Meeting of Stockholders are incorporated by reference into Part III hereof.



TABLE OF CONTENTS

PART I

ITEM 1.	<u>BUSINESS</u>	1
ITEM 1A.	<u>RISK FACTORS</u>	35
ITEM 1B.	<u>UNRESOLVED STAFF COMMENTS</u>	46
ITEM 2.	<u>PROPERTIES</u>	46
ITEM 3.	<u>LEGAL PROCEEDINGS</u>	46
ITEM 4.	<u>MINE SAFETY DISCLOSURES</u>	46

PART II

ITEM 5.	<u>MARKET FOR THE REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES</u>	46
ITEM 6.	<u>SELECTED FINANCIAL DATA</u>	48
	<u>MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND</u>	
ITEM 7.	<u>RESULTS OF OPERATIONS</u>	49
ITEM 7A.	<u>QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK</u>	62
ITEM 8.	<u>FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA</u>	62
	<u>CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND</u>	
ITEM 9.	<u>FINANCIAL DISCLOSURE</u>	62
ITEM 9A.	<u>CONTROLS AND PROCEDURES</u>	62
ITEM 9B.	<u>OTHER INFORMATION</u>	63

PART III

ITEM 10.	<u>DIRECTORS, EXECUTIVE OFFICERS, AND CORPORATE GOVERNANCE</u>	63
ITEM 11.	<u>EXECUTIVE COMPENSATION</u>	63
	<u>SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND</u>	
ITEM 12.	<u>RELATED STOCKHOLDERS</u>	63
	<u>CERTAIN RELATIONSHIPS, RELATED TRANSACTIONS AND DIRECTORS</u>	
ITEM 13.	<u>INDEPENDENCE</u>	63
ITEM 14.	<u>PRINCIPAL ACCOUNTANT FEES AND SERVICES</u>	63

PART IV

ITEM 15.	<u>EXHIBITS AND FINANCIAL STATEMENT SCHEDULES</u>	63
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	<u>SIGNATURE</u>	67
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	<u>INDEX TO FINANCIAL STATEMENTS AND SCHEDULES</u>	F-1
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## FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, and we intend that such forward-looking statements be subject to the safe harbors created thereby. For this purpose, any statements contained in this Annual Report on Form 10-K except for historical information may be deemed to be forward-looking statements. Without limiting the generality of the foregoing, words such as “may,” “will,” “expect,” “believe,” “anticipate,” “intend,” “could,” “estimate,” or “continue” or the negative or other variations thereof or comparable terminology are intended to identify forward-looking statements. In addition, any statements that refer to projections of our future financial performance, trends in our businesses, or other characterizations of future events or circumstances are forward-looking statements.

The forward-looking statements included herein are based on current expectations of our management based on available information and involve a number of risks and uncertainties, all of which are difficult or impossible to predict accurately and many of which are beyond our control. As such, our actual results may differ significantly from those expressed in any forward-looking statements. Factors that may cause or contribute to such differences include, but are not limited to, those discussed in more detail in Item 1 (Business) and Item 1A (Risk Factors) of Part I and Item 7 (Management’s Discussion and Analysis of Financial Condition and Results of Operations) of Part II of this Annual Report on Form 10-K. Readers should carefully review these risks, as well as the additional risks described in other documents we file from time to time with the Securities and Exchange Commission. In light of the significant risks and uncertainties inherent in the forward-looking information included herein, the inclusion of such information should not be regarded as a representation by us or any other person that such results will be achieved, and readers are cautioned not to place undue reliance on such forward-looking information. Except as may be required by law, we disclaim any intent to revise the forward-looking statements contained herein to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events.

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## PART I

Unless otherwise noted, (1) the terms “Arrowhead” and “Arrowhead Research” refer to Arrowhead Research Corporation, a Delaware corporation, (2) the terms the “Company,” “we,” “us,” and “our,” refer to the ongoing business operations of Arrowhead and its Subsidiaries, whether conducted through Arrowhead or a subsidiary of Arrowhead, (3) the term “Subsidiaries” refers collectively to Arrowhead Madison Inc. (“Arrowhead Madison”), Arrowhead Australia Pty Ltd (“Arrowhead Australia”), and Ablaris Therapeutics, Inc. (“Ablaris”), (4) the term “Common Stock” refers to Arrowhead’s Common Stock, (5) the term “Preferred Stock” refers to Arrowhead’s Preferred Stock and the term “Stockholder(s)” refers to the holders of Arrowhead Common Stock.

### ITEM 1. BUSINESS

#### Description of Business

Arrowhead Research develops novel drugs to treat intractable diseases by silencing the genes that cause them. Using the industry’s broadest portfolio of RNA chemistries and efficient modes of delivery, Arrowhead therapies trigger the RNA interference mechanism to induce rapid, deep and durable knockdown of target genes. RNA interference (RNAi) is a mechanism present in living cells that inhibits the expression of a specific gene, thereby affecting the production of a specific protein. Deemed to be one of the most important recent discoveries in life science with the potential to transform medicine, the discoverers of RNAi were awarded a Nobel Prize in 2006 for their work. Arrowhead’s RNAi-based therapeutics leverage this natural pathway of gene silencing to target and shut down specific disease causing genes.

#### Platform Delivery Technology

The Dynamic Polyconjugate™ (DPC™) platform is an RNAi delivery system that promotes high levels of target gene knockdown. The DPC™ platform is engineered specifically to induce efficient endosomal escape, which is the most important differentiating feature of our proprietary technology. The liver targeted DPC™ delivery system has been used in multiple clinical trials and appears to be well tolerated using a variety of RNAi trigger molecules. The DPC™ platform is a modular system that can be optimized on a target-by-target basis, including the ability to target multiple organ systems and cell types outside of the liver.

#### Clinical Stage Drugs

- ARC-520 is an RNAi-based therapeutic designed to treat chronic hepatitis B virus (HBV) infection by reducing the expression and release of new viral particles and key viral proteins with the goal of achieving a functional cure for HBV. The Company is conducting multiple Phase 2b clinical efficacy studies.
- ARC-AAT is a novel unlocked nucleobase analog (UNA)-containing RNAi-based therapeutic for the treatment of liver disease associated with Alpha-1 Antitrypsin Deficiency (AATD), a rare genetic disease that can severely damage the liver and lungs of affected individuals. The goal of treatment with ARC-AAT is to reduce the production of the mutant Z-AAT protein to prevent and potentially reverse accumulation-related liver injury and fibrosis. The Company is conducting a Phase 1b clinical trial.

#### Pre-clinical Stage Drug Candidates

- ARC-521 is a new RNAi-based therapeutic in Arrowhead’s HBV portfolio that was developed to target both cccDNA derived mRNA transcripts, like ARC-520, as well as those from HBV DNA that has integrated into the host DNA. It is intended to address specific patient populations that are predicted to have higher ratios of integrated DNA versus cccDNA. The Company plans to begin clinical studies of ARC-521 in mid-2016.

- ARC-F12 is an RNAi-based therapeutic designed to reduce the production of factor 12 with the goal of providing a prophylactic treatment for hereditary angioedema (HAE) and thromboembolic diseases. Arrowhead is studying relevant disease models, and is considering other potential studies to support advancement of ARC-F12 into clinical trials.
- ARC-HIF2 is an RNAi-based therapeutic designed to reduce the production of hypoxia-inducible factor 2 (HIF-2 ) to treat clear cell renal cell carcinoma. It is the first drug candidate using a new DPC™ delivery vehicle designed to target tissues outside of the liver. Arrowhead is conducting studies in tumor models and is working on manufacturing scale up for the new delivery vehicle to support advancement of ARC-HIF2 into IND-enabling studies.
- ARC-LPA is an RNAi-based therapeutic designed to reduce production of apolipoprotein A (apo(a)), a key component of lipoprotein(a) (Lp(a)), which has been genetically linked with increased risk of cardiovascular diseases. ARC-LPA employs Arrowhead's new hepatic delivery format being developed for subcutaneous administration. This program has not yet been designated by Arrowhead as entering pre-IND development.



## Recent Events

Arrowhead made significant progress on product and platform development during fiscal year 2015 with an expanding pipeline of RNAi therapeutics based on the Dynamic Polyconjugate (DPC™) delivery system. The following are highlights of this progress:

- Strengthened management team and R&D staff with select key hires and expanded internal capabilities in manufacturing, RNA synthesis, toxicology, QA, program management, and clinical and regulatory operations
- Presented data on ARC-520 and ARC-AAT at AASLD Liver Meeting® 2014  
ARC-520 showed statistically significant reduction in HBsAg through day 43 after a single injection ( $p < 0.05$ )  
Repeat dosing of ARC-AAT in primates showed reduction of approximately 90% of serum alpha 1 antitrypsin (AAT) with long duration of effect suggesting that monthly or less frequent dosing may be sufficient for sustained suppression of hepatic AAT production  
ARC-AAT abstract highlighted in the AASLD President's Press Conference as a promising new treatment
- Filed for regulatory approval to begin a Phase 1 clinical trial of ARC-AAT for the treatment of liver disease associated with alpha-1 antitrypsin deficiency
  - Submitted an Investigational New Drug (IND) application to the U.S. Food and Drug Administration and submitted additional clinical trial authorization applications with regulatory authorities in various jurisdictions in Europe, Asia, and Australia/New Zealand for ARC-520
- Initiated dosing in a Phase 1 clinical trial of ARC-AAT
- Acquired Novartis Institutes for BioMedical Research, Inc (“Novartis”) entire RNAi research and development portfolio and associated assets, including:  
Multiple patent families covering RNAi-trigger design rules and modifications that fall outside of key patents controlled by competitors, which the Company believes provides freedom to operate for any target and indication  
Novel intracellular targeting ligands that enhance the activity of RNAi-triggers by targeting the RNA-induced silencing complex (RISC) more effectively and improving stability once RISC is loaded  
An assignment of Novartis' license from Alnylam Pharmaceuticals, Inc. (“Alnylam”) granting Arrowhead access to Alnylam intellectual property, excluding delivery, for 30 gene targets chosen by Novartis  
A pipeline of three candidates initiated by Novartis and for which Novartis has developed varying amounts of preclinical data
- Initiated dosing in Heparc-2004, a multiple-dose Phase 2b clinical study of ARC-520 in the U.S.
- Published new data in the Journal of Controlled Release, 209 (2015) 57-66, on a subcutaneously administered formulation of its DPC™ delivery system
- Completed dosing of Part A of the ARC-AAT phase 1 study in healthy volunteers, and transitioned the study into Part B in patients with PiZZ genotype alpha-1 antitrypsin deficiency
- Presented data at the TIDES Conference on the development of ARC-F12, an RNAi therapeutic for factor 12 (F12) mediated hereditary angioedema and thromboembolic diseases
- Received Orphan Drug Designation from the United States Food and Drug Administration
- Initiated multiple-dose Heparc-2002 and Heparc-2003 Phase 2b studies of ARC-520 in Europe and Asia

- Expanded Part B of the Phase 1 study of ARC-AAT to include additional treatment sites in Europe, Australia, and New Zealand
  - Nominated ARC-HIF2 against clear cell renal cell carcinoma as Arrowhead's first therapeutic candidate delivered using a new DPC™ designed to target tissues outside of the liver
  - Hosted an analyst day to discuss top-line findings from the Heparc-2001 Phase 2a clinical study of ARC-520 and findings from a study of 9 chimpanzees that have been treated monthly with ARC-520 for between 6 and 11 months. Key messages included the following:
    - Arrowhead's proprietary DPC™ platform can effectively and consistently knock down target genes in humans
    - ARC-520 achieves significant HBV s-Antigen (HBsAg) reductions in humans, particularly in treatment naïve, HBeAg-positive patients
    - Arrowhead identifies a large target HBV population for ARC-520 and describes a new paradigm for the HBV lifecycle
    - ARC-520 induces deep HBsAg reduction in chronically HBV infected chimps
    - ARC-520 has been well tolerated
    - Arrowhead expands its HBV portfolio by nominating an additional clinical candidate that is complementary to ARC-520
  - Presented data on ARC-LPa against cardiovascular disease, which uses a new subcutaneous delivery construct that Arrowhead has developed
  - Presented data at the AASLD Liver Meeting 2015 including the following:
    - ARC-520 led to robust, sustained anti-viral effects in chimpanzees with chronic HBV and also described an important new discovery that HBV DNA integrated into the host genome is likely an important source of HBV surface antigen (HBsAg) production
    - In a Phase 2a clinical study, ARC-520 effectively reduced HBV viral antigens derived from cccDNA. HBV surface antigen (HBsAg) was reduced substantially with a maximum reduction of 1.9 logs (99%) and a mean maximum reduction of 1.5 logs (96.8%) in treatment naïve e-antigen (HBeAg)-positive patients
  - Presented data at Hep DART 2015 showing that ARC-520 led to immune reactivation in 7 of 9 chimps with chronic hepatitis B infection
- Acquisition of Roche and Novartis RNAi business and assets

The last four years have brought substantial change to Arrowhead's research and development (R&D) capabilities and strategy. We are now an integrated RNAi therapeutics company, developing novel drugs that silence disease causing genes based on our broad RNAi technology platform.

The most significant step in this transition was our 2011 acquisition of the RNAi therapeutics business of Hoffmann-La Roche, Inc. and F. Hoffmann-La Roche Ltd. (collectively, "Roche"), which included the DPC™ delivery system that we have used for all our clinical drug candidates to date. Roche built this business unit in a manner that only a large pharmaceutical company is capable of: backed by expansive capital resources, Roche systematically acquired technologies, licensed expansive intellectual property rights, attracted leading scientists, developed new technologies internally, and built state-of-the-art facilities. At a time when the markets were questioning whether RNAi could become a viable therapeutic modality, we saw great promise in the technology broadly and the quality of what Roche built specifically. The acquisition provided us with three primary sources of value:

- Broad freedom to operate with respect to key patents directed to the primary RNAi-trigger formats: canonical, UNA, meroduplex, and dicer substrate structures;
- A best-in-class RNAi delivery system, which we believe to be the targetable DPC™ platform; and

- A state-of-the-art R&D facility in Madison, Wisconsin, including a large team of scientists experienced in RNAi and oligonucleotide delivery.

In addition, in March 2015 we acquired the entire RNAi research and development portfolio and associated assets of Novartis. Novartis had been working in the RNAi field for over a decade and made some very important advancements in their developments of proprietary oligonucleotide formatting and modifications. Key aspects of the acquisition include the following:

- Multiple patent families covering RNAi-trigger design rules and modifications that fall outside of key patents controlled by competitors, which we believe provides freedom to operate for any target and indication;
- Novel intracellular targeting ligands that enhance the activity of RNAi-triggers by targeting the RNA-induced silencing complex (RISC) more effectively and improving stability once RISC is loaded;
- An assignment of Novartis' license from Alnylam Pharmaceuticals, Inc. (“Alnylam”) granting Arrowhead access to certain Alnylam intellectual property, excluding delivery, for 30 gene targets; and
- A pipeline of three candidates initiated by Novartis for which Novartis has developed varying amounts of preclinical data.

We see the Roche and Novartis acquisitions as a powerful combination of intellectual property, R&D infrastructure, and RNAi delivery experts. We believe we are the only company with access to all primary RNAi-trigger structures now including additional novel structures discovered by Novartis. This enables us to optimize our drug candidates on a target-by-target basis and use the structure and modifications that yield the most potent RNAi trigger. In addition, our DPC™ delivery system enables us to deliver our drug candidates efficiently to hepatocytes and to non-hepatic tissues in a highly specific manner. Our R&D team and facility enable rapid innovation and drive to the clinic, as evidenced by the speed at which we have advanced our pipeline to now include six proprietary drug candidates in a very short period of time.

We have focused our resources primarily on the DPC™ platform and on advancing our proprietary DPC™-enabled RNAi therapeutic candidates through clinical trials. Additionally, with our increased R&D headcount, Arrowhead now has the infrastructure, expertise, IP portfolio, chemistry, manufacturing and control (CMC) capabilities, and management that we believe is necessary to support potential partnerships and research collaborations with large biopharma companies from discovery stage through commercialization.

#### Pipeline Overview

Our internal preclinical and clinical development programs are designed to create value directly through our proprietary candidates. These programs also drive value to the technology platform as proof of concept for the power of the programs to enable innovative new therapies.

## Clinical Trials

The following table serves as a summary of our ongoing and completed clinical trials as of September 30, 2015:

Drug	Study Name	Stage	Status	Description	ClinicalTrials.gov Identifier
ARC-520	Heparc-1001	Phase 1	Enrollment Complete	Single dose escalation study in healthy volunteers to evaluate safety and tolerability of ARC-520	NCT01872065
	Heparc-1002	Phase 1	Enrolling	Single dose study to evaluate tolerability of increasing infusion rates of ARC-520	NCT02535416
	Heparc-2001	Phase 2a	Enrollment Complete	Single dose escalation study in HBV patients to evaluate reduction in viral antigens in response to ARC-520	NCT02065336
	Heparc-2001 OLE	Phase 2a	Enrolling	Open label multi-dose extension study in patients completing Heparc-2001	NCT02065336
	Heparc-2002	Phase 2b	Enrolling	Multi-dose study to determine the depth of hepatitis B surface antigen (HBsAg) reduction in response to ARC-520 in combination with entecavir or tenofovir in hepatitis B envelope antigen (HBeAg) negative patients	NCT02604199
	Heparc-2003	Phase 2b	Enrolling	Multi-dose study to determine the depth of HBsAg reduction in response to ARC-520 in combination with entecavir or tenofovir in HBeAg positive patients	NCT02604212
	Heparc-2004	Phase 2b	Enrolling	Multi-dose study to determine the depth of HBsAg reduction in response to ARC-520 in combination with entecavir or tenofovir in HBeAg positive patients	NCT02452528
	Heparc-2008 (MONARCH)	Phase 2b	Not Yet Enrolling	Open label multi-dose study to evaluate ARC-520 alone and in combination with other therapeutics in patients with chronic HBV	NCT02577029
	ARC-AATARCAAT-1001	Phase 1a/1b	Enrolling	Single dose escalation study to determine the safety, tolerability and effect on circulating alpha-1 antitrypsin levels of ARC-AAT in healthy volunteers and patients	NCT02363946
	Internal Clinical Programs – ARC-520				

## ARC-520 – Hepatitis B Virus Infection

ARC-520 is an RNAi therapeutic candidate for the treatment of chronic hepatitis B infection with the goal of achieving a functional cure. It is the first clinical candidate to use our proprietary DPC™ technology and includes two siRNA duplexes, each conjugated to a cholesterol derivative to enhance liver delivery and cellular uptake. We have designed ARC-520 to be co-administered with an active excipient, a masked, hepatocyte targeted polymeric amine (the DPC™ delivery system).

Figure 1: ARC-520 schematic

We see the need for a next generation HBV treatment with a finite treatment period and an attractive dosing regimen, and that can be used at earlier stages of disease. We believe a novel therapeutic approach such as this that can effectively treat or provide a functional cure (seroclearance of HBsAg and with or without development of excess patient antibodies against HBsAg) has the potential to take significant market share and may expand the available market to include patients that are currently untreated.

Chronic Hepatitis B Virus

According to the World Health Organization, 360 million people worldwide are chronically infected with hepatitis B virus, of which 500,000 to 1,000,000 people die each year from HBV related liver disease. Chronic HBV infection is defined by the presence of hepatitis B surface antigen (HBsAg) for more than 6 months. In the immune tolerant phase of chronic infection, which can last for many years, the infected person typically produces very high levels of viral DNA and viral antigens. However, the infection is not cytotoxic and the carrier may have no symptoms of illness. Over time, the ongoing production of viral antigens causes inflammation and necrosis, leading to elevation of liver enzymes such as alanine and aspartate transaminases, hepatitis, fibrosis, and liver cancer (hepatocellular carcinoma, or HCC). If untreated, as many as 25% to 40% of chronic HBV carriers ultimately develop cirrhosis or HCC. Antiviral therapy is generally prescribed when liver enzymes become elevated.

## Current Treatments

The current standard of care for treatment of chronic HBV infection is a daily oral dose of nucleotide/nucleoside analogs (NUCs) or a regimen of interferon injections for approximately one year. NUCs are generally well tolerated, but patients may need lifetime treatment because viral replication often rebounds upon cessation of treatment. Interferon therapeutics can result in a functional cure in 10-20% of some patient types, but treatment is often associated with significant side effects, including severe flu-like symptoms, marrow suppression, and autoimmune disorders.

## Goal of ARC-520 Treatment

ARC-520 is designed to silence the production of all HBV gene products with the goal of achieving a functional cure. The siRNAs in ARC-520 target multiple components of HBV production including the pregenomic RNA that would be reverse transcribed to generate the viral DNA. The siRNAs intervene at the mRNA level, upstream of where NUCs act, and target the mRNAs that produce HBsAg proteins, the viral polymerase, the core protein that forms the capsid, the pre-genomic RNA, the HBeAg, and the hepatitis B X antigen (HBxAg). NUCs are effective at reducing production of viral particles, but are ineffective at controlling production of HBsAg and other HBV gene products. Arrowhead believes that a reduction in the production of HBsAg and other proteins that NUCs are ineffective at controlling is necessary to effective HBV therapy, because those proteins are thought to be major contributors to repression of the immune system and the persistence of liver disease secondary to HBV infection.

Figure 2: Chronic HBV mechanism untreated

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Figure 3: Mechanism of action NUCs

Figure 4: Mechanism of action ARC-520

8

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## Nonclinical Data

Efficacy data in mouse models of HBV infection show that ARC-520 is capable of reducing HBsAg by greater than 3 log (99.9%), HBV DNA by approximately 3 logs, and HBeAg to the limit of detection. Pharmacologic effects persist for approximately one month after a single dose of ARC-520 in mice models. Safety data in rodents and non-human primates indicate an acceptable safety margin. Preclinical data in a chimpanzee chronically infected with HBV demonstrate that intravenous administration of two doses (2 mg/kg on day 1, and 3 mg/kg on day 15) of ARC-520 resulted in substantial and sustained reductions in HBV DNA, HBeAg, and HBsAg, which did not return to baseline until study day 43, 43, and 71, respectively. In addition, an increase in serum alanine transaminase (ALT) occurred 4 weeks after the second dose, coincident with the nadir of circulating HBsAg. This is suggestive of a therapeutic immunological flare, which is thought to be part of a cascade that under chronic therapy may lead to HBsAg seroclearance and functional cure. Observed increases in key chemokine/cytokine mRNAs are also consistent with a T-cell mediated immunological event.

Additional nonclinical data from a multiple dose study in 9 chimpanzees were reported in 2015. At the start of the study, five chimpanzees were HBeAg-positive and four chimpanzees were HBeAg-negative. Deep sequencing and phylogenetic analyses indicated the HBV sequence was a chimpanzee variant of human HBV. To reduce viral replication prior to treatment with ARC-520, chimpanzees were treated for 8-24 weeks with entecavir (ETV) or ETV+tenofovir (TDF) in one case. Following the lead-in period, animals were administered ARC-520 intravenously at 4-week intervals. Dose levels administered were 2, 3, or 4 mg/kg ARC-520, along with maintenance doses of ETV or ETV+TDF.

The study showed a robust, sustained direct anti-viral effect on HBsAg production in all HBeAg-positive and -negative chimpanzees during ARC-520 treatment. One chimpanzee achieved sustained virologic response (SVR) off-therapy and two chimpanzees exhibited signs of immune reactivation. HBeAg-positive chimpanzees displayed the highest levels of HBsAg knockdown - up to 2.7 log. In HBeAg-negative chimpanzees, HBsAg knockdown was also substantial - up to 0.9 log. ARC-520 was well tolerated after multiple doses up to 4 mg/kg ARC-520 (highest dose tested). Evidence indicates integrated HBV DNA is a significant source of total HBsAg, especially in HBeAg-negative chimpanzees.

### Phase 1 (Heparc-1001)

Arrowhead completed nine dose cohorts in the Heparc-1001 Phase 1 trial in 2014. The study was designed to characterize the safety profile of ARC-520 across a range of doses and evaluate pharmacokinetics. It was a single-center, randomized, double-blind, placebo-controlled, single dose-escalation, first-in-human study of ARC-520 administered intravenously to healthy adult volunteers. All subjects received either placebo or ARC-520 in doses ranging from 0.01 mg/kg to 4 mg/kg. The study successfully enrolled all 54 subjects (36 received ARC-520, 18 placebo) at a single center in Melbourne, Australia.

There have been no reports of serious adverse events (SAEs), no dose limiting toxicities, no discontinuations due to adverse events (AEs), and a modest overall occurrence rate of AEs without a clear dose-related increase in frequency or severity. There has been a modest occurrence rate of non-clinically significant abnormal laboratory tests. There were no reported drug related or clinically significant differences for vital signs or ECGs between subjects receiving drug versus placebo. One arrhythmia noted on telemetry occurred in a subject with similar previously undiagnosed prior cardiac atrial rhythm abnormalities and one occurrence of hypotension that appears to have been artifact from a failing automated blood pressure machine.

One occurrence each of moderate flushing and urticarial rash seen at dose levels of 0.3 mg/kg and 2.0 mg/kg respectively led to the subsequent reduction, by half, in infusion rate of ARC-520 as well as the introduction of pretreatment with an oral over-the-counter antihistamine. Since the introduction of these mitigations, no additional signs of hypersensitivity or infusion reactions have been seen.



There were mild creatinine elevations in 6% of subjects receiving ARC-520 and 6% receiving placebo, which were transient with rapid (<24 hours) return to baseline. There were no signs of tubular damage on laboratory evaluation and these subjects had no additional clinical symptoms. Overall, the changes in creatinine are similar between ARC-520 and placebo groups and thought to be, at least primarily, due to dietary intake of protein. There were no changes in ALT, AST or CK considered to be clinically significant by the study investigator.

In summary, ARC-520, when administered as a single dose up to 4 mg/kg to healthy volunteers, appears to be well tolerated. The table below shows the incidence of treatment emergent adverse events observed in greater than 5% of subjects.

Adverse Events >5%		
	Placebo (n=18)	ARC-520 (n=36)
All Attributions		
All AEs	67%	67%
Mild	72%	69%
Moderate	28%	31%
Severe	0%	0%
Headache	33%	14%
URI	28%	19%
Somnolence	6%	8%
Lethargy	6%	6%
Creatinine increase	6%	6%
Myalgia	0%	6%
Dizziness	0%	6%

Figure 5: Phase 1 AE reporting

Phase 2a (Heparc-2001)

In 2015 Arrowhead reported data from the Heparc-2001 Phase 2a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study designed to determine the depth and duration of hepatitis B surface antigen (HBsAg) reduction after administration of ARC-520 in combination with entecavir in patients with chronic HBV infection. Secondary objectives included the assessment of safety and tolerability of escalating single doses of ARC-520 co-administered with a fixed dose of entecavir and multiple additional secondary and exploratory endpoints. Significant details about the seven cohorts are included below.

Cohort	Prior entecavir (ETV)	Patient Type	ARC-520 dose	Active/Placebo	Baseline HBsAg Mean (range) Log IU/mL	Status
1	Yes	HBeAg-neg	1.0 mg/kg	6/2	3.4 (3.0-4.2)	Complete/Unblinded
2	Yes	HBeAg-neg	2.0 mg/kg	6/2	3.5 (3.2-4.3)	Complete/Unblinded
3	Yes	HBeAg-neg	3.0 mg/kg	6/2	3.6(3.1-4.0)	Complete/Unblinded
4	Yes	HBeAg-neg	4.0 mg/kg	6/2	3.4 (3.2-4.0)	Complete/Unblinded
5	Yes	HBeAg-pos	4.0 mg/kg	6/2	3.6 (3.1-4.2)	Complete/Unblinded
6*	Yes	HBeAg-pos	2 x 2.0 mg/kg (two weeks apart)	6/0	3.3 (3.0-3.6)	Complete/Open label
7	No	HBeAg-pos	4.0mg/kg	6/0	4.0 (0.8-4.9)	Ongoing / Openlabel
		HBeAg-neg		6/0	2.9 (1.0-3.6)	

Figure 6: Phase 2a dose cohorts

In connection with Heparc-2001, fifty-eight patients were successfully dosed with 48 receiving the drug and 10 receiving a placebo. 20 females and 38 males were enrolled, all of Chinese ethnicity, with a mean age of 41 years

(range of 23 to 59). Topline results were reported at an analyst and investor day hosted by the Company and additional details were presented at the 2015 AASLD Liver Meeting. To date there have been no serious AEs, no dose limiting toxicities, no discontinuations due to medication AEs, and a modest occurrence rate of AEs. All reported AEs were deemed unrelated to study drug by the principal investigator. Safety labs continue to lack indication of end organ toxicity, with a low occurrence rate of abnormal laboratory tests with no observed relationship to timing or dose.

Adverse Events	1 mg/kg (N=6)	2mg/kg (N=6)	3 mg/kg (N=6)	4 mg/kg (N=24)	2 mg/kg x2 (N=6)	Placebo (N=10)
All AEs	1	5	1	2	1	0
Extravasation		1 mild				
Malaise		1 mod				
Influenza	1 mild					
Blood CK increase		1 mild				
Diabetes Mellitus		1 mild				
Pain in extremity			1 mild			
Presyncope		1 mod				
Headache				1 mild		
Dizziness				1 mild		
Fever					1 mild	

Figure 7: Phase 2a AE reporting

Arrowhead measured the Log reduction of quantitative HBsAg, HBcrAg, and HBeAg from baseline as an assessment of ARC-520 activity. This is the first time that a reduction in HBsAg, HBcrAg, and HBeAg mediated through RNA interference has been reported in chronic HBV patients. In this study, ARC-520 effectively inhibited cccDNA-derived mRNA with reductions up to 1.9 logs (99%). ARC-520 had a direct antiviral effect that lasted up to 57 days after a single dose. In patients exhibiting a delayed response, duration of over 85 days was observed. The best qHBsAg reduction was seen in treatment naïve HBeAg-positive patients. HBeAg-negative patients showed a delayed response. HBeAg-negative, ETV experienced patients showed a dose response in HBcrAg but qHBsAg dose response was less pronounced. HBeAg positive, ETV experienced patients had a substantially higher reduction in HBeAg and HBcrAg compared to HBsAg. Variations in viral antigen reduction are consistent with lower levels of cccDNA derived mRNA transcripts in chronic ETV patients and HBeAg negative patients. These data are summarized in the figures below.

		Log reduction from baseline			
		Mean (max)			
Cohort	Dose	HBeAg	Prior HBsAg	HBcrAg	HBeAg
	(mg/kg)	status	ETV		
1	1	Neg	Y	-0.2 (-0.3)*	-0.2 (-0.2) N/A
2	2	Neg	Y	-0.2 (-0.3)*	-0.5 (-0.5) N/A
3	3	Neg	Y	-0.3 (-0.4)*	-0.4 (-0.7) N/A
4	4	Neg	Y	-0.4 (-0.5)*	-0.9 (-1.1) N/A
5	4	Pos	Y	-0.3 (-0.7)*	-0.9 (-1.1) -1.2 (-1.7)
6‡	2x2	Pos	Y	-0.5 (-0.8)+	-0.7 (-1.2) Pending
7‡, †	4	Pos	N	-1.5 (-1.9)+	Pending Pending
7‡	4	Neg	N	-0.2 (-0.8)+	Pending N/A

\*Roche Elecsys batch analyzed data set +Abbott Architect data ‡Preliminary data, analysis is ongoing †Excluding transitional patient

Figure 8: Max reduction in viral antigens

Figure 9: Mean reduction in HBsAg in treatment naive patients (cohort 7)

Phase 2b

Multiple dose and combination studies of ARC-520 aimed at producing functional cures are underway. These studies include Heparc-2001 open label extension, Heparc-2002, Heparc-2003, Heparc-2004, and the MONARCH study (Heparc-2008). There are clinical sites for these studies in the US, Europe, Asia, and Australia/New Zealand.

12

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## Internal Clinical Programs – ARC-AAT

### ARC-AAT – Liver Disease Associated with Alpha-1 Antitrypsin Deficiency

Arrowhead has developed a therapeutic candidate (ARC-AAT) for the treatment of liver disease associated with Alpha-1 Antitrypsin Deficiency (AATD), a rare genetic disease that severely damages the liver and lungs of affected individuals. ARC-AAT employs a novel unlocked nucleobase analog (UNA)-containing RNAi molecule designed for systemic delivery using the DPC™ delivery system. Pre-clinical studies have demonstrated that ARC-AAT is highly effective at knocking down the Alpha-1 antitrypsin (AAT) gene transcript and reducing the hepatic production of the mutant AAT protein.

#### Figure 10: ARC-AAT schematic Alpha-1 Antitrypsin Deficiency

AATD is a genetic disorder associated with liver disease in children and adults and pulmonary disease in adults. AAT is a circulating glycoprotein protease inhibitor that is primarily synthesized and secreted by liver hepatocytes. Its physiologic function is the inhibition of neutrophil proteases to protect healthy tissues during inflammation and prevent tissue damage. The most common disease variant, the Z mutant, has a single amino acid substitution that results in improper folding of the protein. The mutant protein cannot be effectively secreted and accumulates in globules in the hepatocytes. This triggers continuous hepatocyte injury, leading to fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma.

#### Current Treatments

Individuals with the homozygous PiZZ genotype have severe deficiency of functional AAT leading to pulmonary disease and hepatocyte injury and liver disease. Lung disease is frequently treated with AAT augmentation therapy. However, augmentation therapy does nothing to treat liver disease, and there is no specific therapy for hepatic manifestations. There is a significant unmet need as liver transplant, with its attendant morbidity and mortality, is currently the only available cure.

#### Goal of ARC-AAT Treatment

The goal of treatment with ARC-AAT is prevention and potential reversal of Z-AAT accumulation-related liver injury and fibrosis. Reduction of inflammatory Z-AAT protein, which has been clearly defined as the cause of progressive liver disease in AATD patients, is important as it is expected to halt the progression of liver disease and allow fibrotic tissue repair.

#### Preclinical Data

In preclinical studies with PiZ mice, which are genetically modified to produce the mutant human AAT (Z-AAT), ARC-AAT induced a greater than 95 percent reduction in circulating AAT after a single dose. The addition of chemical modifications, including UNAs, slowed the rebound in production of AAT compared to canonical siRNAs, and produced a substantially improved duration of effect.

After eight weeks of treatment in multi-dose studies in PiZ mice, soluble (monomeric) and insoluble (polymeric) forms of Z-AAT were greatly reduced in the livers of PiZ mice treated with ARC-AAT. In addition, liver globule burden was substantially reduced from baseline levels and in comparison to treatment with saline, which showed progressive globule formation (shown in the figure below). These data were submitted as an abstract to the 2014 AASLD Liver Meeting and selected for presentation at this conference.

Baseline	AAT-UNA q2w	Saline
5 weeks old		
	13 weeks old	13 weeks old

Figure 11: Reduction in Z-AAT globules in livers of PiZ mice

In primate studies, knockdown of AAT in serum persisted for over ten weeks with greater than 80 percent knockdown observed at the six-week time point. Multi-dose studies in primates showed a sustained reduction of AAT with once every six weeks dosing, suggesting that once monthly or less frequent dosing is sufficient to maintain ~80-90% knockdown (shown in the figure below).

Figure 12: Long term reduction of AAT in NHPs following repeat dosing with ARC-AAT

(ARC-EX1 is a DPC™ delivery system)

## The Alpha-1 Project

Arrowhead has an agreement with The Alpha-1 Project (TAP), the venture philanthropy subsidiary of the Alpha-1 Foundation. TAP's mission is to support organizations in pursuit of cures and therapies for lung and liver disease caused by Alpha-1 Antitrypsin Deficiency. Under the terms of the agreement, TAP will partially fund the development of ARC-AAT. In addition to the funding, TAP will make its scientific advisors available to Arrowhead, assist with patient recruitment for clinical trials with its Alpha-1 Foundation Patient Research Registry, and engage in other collaborative efforts that support the development of ARC-AAT.

### Phase 1

Arrowhead is conducting a single dose Phase 1 clinical study of ARC-AAT. The study is a multi-center, randomized, placebo-controlled, double-blind, single dose-escalation, first-in-human study to evaluate the safety, tolerability and pharmacokinetics of ARC-AAT and the effect on circulating AAT levels. The study has been enrolling dose cohorts of six participants each, with participants randomized at a ratio of 2:1 (active:placebo) to receive a single intravenous injection of either ARC-AAT or placebo (normal saline). The study consists of two parts; Part A in healthy volunteers and part B currently being conducted in patients with PiZZ genotype AATD. Dosing in patients (part B) began at a dose level used in healthy volunteers that met pre-defined criteria for AAT knockdown and then continued dose escalation may proceed under the protocol. The study evaluates participants for 28 days following dosing, with additional follow-up if needed every 2 weeks until AAT levels return to baseline.

### Orphan Drug Designation

In June 2015, Arrowhead was granted the orphan drug designation for ARC-AAT by the U.S. Food and Drug Administration (FDA). Orphan drug designation provides incentives for sponsors to develop products for rare diseases. These incentives include increased engagement with FDA on drug development activities, exemption from all future product-specific regulatory fees, the opportunity to apply for R&D funding, tax credits, an increased chance of priority review, and 7 years of orphan exclusivity at the time of New Drug Application (NDA).

### Preclinical Programs

In addition to our clinical candidates, we are actively engaged in the discovery and development of additional pre-clinical stage products for intravenous and subcutaneous administered therapeutics targeting the liver, as well as programs targeting extra-hepatic tissues. We focus on disease targets that are well suited for intervention with targeted RNAi therapeutics using our DPC™ delivery platform.

### ARC-521

ARC-521 is a new RNAi-based therapeutic in Arrowhead's HBV portfolio that was developed to target both cccDNA derived mRNA transcripts, like ARC-520, as well as those from HBV DNA that has integrated into the host DNA. It is intended to address specific patient populations that are predicted to have higher ratios of integrated DNA versus cccDNA. The Company plans to begin clinical studies of ARC-521 in mid-2016.

### ARC-F12

ARC-F12 is an RNAi-based therapeutic designed to reduce the production of factor 12 with the goal of providing a prophylactic treatment for hereditary angioedema (HAE) and thromboembolic diseases. Arrowhead is conducting relevant disease models, and is considering other potential studies to support advancement of ARC-F12 into clinical trials.

### ARC-HIF2



ARC-HIF2 is an RNAi-based therapeutic designed to reduce the production of hypoxia-inducible factor 2 (HIF-2 ) to treat clear cell renal cell carcinoma. It is the first drug candidate using a new DPC™ delivery vehicle designed to target tissues outside of the liver. Arrowhead is conducting tumor models and is working on manufacturing scale up for the new delivery vehicle to support advancement of ARC-HIF2 into IND-enabling studies.

#### ARC-LPA

ARC-LPA is an RNAi-based therapeutic designed to reduce production of apolipoprotein A (apo(a)), a key component of lipoprotein(a) (Lp(a)), which has been genetically linked with increased risk of cardiovascular diseases. ARC-LPA employs Arrowhead's new hepatic delivery format being developed for subcutaneous administration. This program has not yet been officially designated by Arrowhead as entering pre-IND development.

#### Partner-based Programs

Alnylam Pharmaceuticals

In January 2012, Arrowhead granted Alnylam a license to utilize the DPC™ delivery technology for a single RNAi therapeutic product. Alnylam is collaborating with Arrowhead to develop this technology for an undisclosed target. Alnylam has not publically disclosed what progress, if any, it may have made with respect to this target. Arrowhead is eligible to receive milestone payments and royalties on worldwide sales.

#### Shire

In December 2012, Arrowhead signed a research collaboration and license agreement with Shire AG (“Shire”) to develop and commercialize targeted peptide-drug conjugates (PDCs) utilizing Arrowhead’s human-derived Homing Peptide platform and Shire’s therapeutic payloads. Arrowhead may receive research funding and could be eligible for development, regulatory, and commercialization milestone payments of up to \$32.8 million for each development candidate, plus additional milestone payments for a second indication, and royalties on worldwide sales.

#### RNA Interference & the Benefits of RNAi Therapeutics

RNA interference (RNAi) is a mechanism present in living cells that inhibits the expression of a specific gene, thereby affecting the production of a specific protein. Deemed to be one of the most important recent discoveries in life science with the potential to transform medicine, the discoverers of RNAi were awarded a Nobel Prize in 2006 for their work. RNAi-based therapeutics may leverage this natural pathway of gene silencing to target and shut down specific disease causing genes.

#### Figure 13: Mechanism of RNA interference

Small molecule and antibody drugs have proven effective at inhibiting certain cell surface, intracellular, and extracellular targets. However, other drug targets such as intranuclear genes and some proteins have proven difficult to inhibit with traditional drug-based and biologic therapeutics. Developing effective drugs for these targets would have the potential to address large underserved markets for the treatment of many diseases. Using the ability to specifically silence any gene, RNAi therapeutics may be able to address previously “undruggable” targets, unlocking the market potential of such targets.

#### Advantages of RNAi as a Therapeutic Modality

- Silences the expression of disease causing genes;

16

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- Potential to address any target in the transcriptome including previously "undruggable" targets;
- Rapid lead identification;
- High specificity;
- Opportunity to use multiple RNA sequences in one drug product for synergistic silencing of related targets; and
- RNAi therapeutics are uniquely suited for personalized medicine through target and cell specific delivery and gene knockdown.

#### Addressing the RNAi Delivery Challenge

To date, the primary challenge to the development of RNAi therapeutics has been delivering the fragile, often immunogenic and otherwise rapidly cleared RNAi trigger molecules, into the cytoplasm of the cell, where RNAi activity occurs. This hurdle has prevented many RNAi therapeutics from reaching their full potential. Many companies have attempted to overcome the delivery challenge. Most early systems involved various carriers such as liposomes. However, development in humans has been limited due to toxicity and immunogenicity of these approaches when studied in clinical trials.

#### The Dynamic Polyconjugate™ RNAi Delivery System

The DPC™ delivery system represents an innovative solution to the RNAi delivery problem, specifically designed to overcome barriers to systemic administration of RNAi trigger molecules. Developed by Arrowhead scientists, the inspiration for DPC™ technology came from the physical characteristics of viruses, nature's own nanoparticles for nucleic acid delivery. Viruses are efficient at finding their target cells and delivering their nucleic acid payload to the proper cellular compartment. Key features of viruses are their small size, their overall negative surface charge, their specificity for particular cell types based on receptors unique to that cell, and their ability to disassemble and release their nucleic acid cargo to the proper cell compartment in response to cellular triggers. All of these features are incorporated into DPC™ technology.

Prototypical DPC delivery systems are small, generally 5-20 nanometers (nm) in size, with an amphipathic polymer backbone. Arrowhead has a library of polymers, enabling optimization based on factors such as preferred mode of administration, pharmacokinetics, and target tissue. Shielding agents such as polyethylene glycol and targeting ligands may be reversibly attached to the polymer backbone. In some constructs, the RNAi trigger payload is attached to the DPC™ delivery system, while in other constructs, the RNAi trigger circulates attached to a different carrier. When attached, the DPC™ delivery system construct protects the RNAi trigger payload while allowing the polymer to circulate in the blood without creating undue toxicity. The targeting ligand guides it to the cell type of interest where, together with the RNAi trigger, it is taken up into a membrane-enclosed cellular compartment known as an endosome. The polymer is selected for its ability to disrupt the endosomal membrane, which allows the RNAi trigger to be released into the cytoplasm. There, it engages the cell's RNAi machinery, ultimately resulting in knockdown of target gene expression. This membrane active chemistry of the DPC™ polymeric backbone is modified, or "masked", using proprietary chemistry until it reaches the endosome where pH changes cause the masking chemistries to fall off. Masking of the polymer's membrane active chemistry accomplishes two interrelated objectives that are critical to in vivo RNAi delivery:

- Reduction of toxicity by controlling when the membrane disruptive property of the polymer is activated; and
- Inhibition of non-specific interactions with blood components and non-targeted cell types.

Figure 14: Single molecule DPCs™

18

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### Co-injection of DPCs™ and RNAi Triggers

Arrowhead has developed multiple forms of the prototypical DPC™ delivery system. ARC-520 and ARC-AAT use a DPC™ formulation whereby the RNAi trigger is conjugated to cholesterol and is not attached to the DPC™. Pre-clinical studies have shown co-injection of the liver-targeted DPC™ polymer together with the RNAi trigger conjugated to a lipophilic moiety, such as cholesterol, results in a greater than 500-fold increase in the potency when compared to the RNAi trigger with cholesterol alone. This formulation retains the potent endosomal escape capabilities of Arrowhead's DPC™ platform, simplifies drug manufacturing, and creates new targeting opportunities.

Figure 15: Mechanism of action for co-injected DPCs

19

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## Subcutaneous Administration of RNAi Therapeutics

Arrowhead has also developed multiple delivery formulations for subcutaneous administration of RNAi therapeutics where the RNAi triggers are conjugated to the delivery vehicle. Using these vehicles, high-level target gene knockdown has been observed in animal studies. Arrowhead intends to utilize a subcutaneous formulation in its ARC-LPA program and in additional programs where chronic dosing may be required.

## Intellectual Property

The Company controls approximately 306 issued patents (including 66 for DPCs; 25 for hydrodynamic gene delivery; 26 for pH labile molecules; 7 for polyampholyte; 5 for template polymerization; 12 for delivery polymers; 133 for RNAi trigger molecules; 1 for targeting molecules; 1 for liver expression vector; and 29 for Homing Peptides), including European validations, and 247 patent applications (108 applications in 13 families for DPCs; 140 applications in 23 families for RNAi trigger targets; and 8 for Homing Peptides). The pending applications have been filed throughout the world, including, in the United States, Argentina, ARIPO (Africa Regional Intellectual Property Organization), Australia, Brazil, Canada, Chile, China, Eurasian Patent Organization, Europe, Hong Kong, Israel, India, Indonesia, Iraq, Jordan, Japan, Republic of Korea, Mexico, New Zealand, OAPI (African Intellectual Property Organization), Peru, Philippines, Russian Federation, Saudi Arabia, Singapore, Thailand, Taiwan, Venezuela, Vietnam, and South Africa.

## RNAi Triggers

The Company owns patents directed to RNAi triggers targeted to reduce expression of hepatitis B viral proteins as well the RRM2 gene.

Patent Group	Estimated Year of Expiration
RNAi Triggers	
Patent directed to HBV RNAi triggers	2032
Patent directed to RRM2 RNAi triggers	2031
-ENaC	2028
-ENaC	2031
-Catenin	2033
KRAS	2033
HSF1	2030, 2032
APOC3	2034
Cx43	2029
HIF1A	2026
FRP-1	2026
HCV	2023
PDtype4	2026
PI4Kinase	2028
HRH1	2027
SYK	2027
TNF-	2027
20	

## Dynamic Polyconjugates

The DPC related patents have issued in the United States, Australia, Canada, Europe, France, Germany, Italy, Spain, Switzerland, United Kingdom, India, Japan, Mexico, New Zealand, Philippines, Russia, South Korea, Singapore, and South Africa. The Company also controls a number of patents directed to hydrodynamic nucleic acid delivery, which issued in the United States, Australia and Europe (validated in Austria, Belgium, Switzerland, Germany, Denmark, Spain, Finland, France, the United Kingdom, Hungary, Ireland, Italy, Netherlands and Sweden). The approximate year of expiration for each of these various groups of patents are set forth below:

Patent Group	Estimated Year of Expiration
Dynamic Polyconjugates™ (DPC™)	
Dynamic Polyconjugates	2027
Dynamic Polyconjugates – second iteration	2031
Membrane Active Polymers	2027
Membrane Active Polymers – Additional Iterations	2024
Membrane Active Polymers – Additional Iterations	2032
Copolymer Systems	2024
Polynucleotide-Polymer Composition	2024
ARC-520 Polymer	2031
ARC-521 Composition	2035
Masking Chemistry	2031
Masking Chemistry	2035
Polyampholyte Delivery	2017
pH Labile Molecules	2020
Endosomolytic Polymers	2020
Hydrodynamic delivery	
First iterations	2015
Second iteration	2020
Third iteration	2024

The RNAi and drug delivery patent landscapes are complex and rapidly evolving. As such, we may need to obtain additional patent licenses prior to commercialization of our candidates. You should review the factors identified in “Risk Factors” in Part I, Item 1A of this Annual Report on Form 10-K.

## Homing Peptides

We also control patents related to our Homing Peptide platforms, related to Adipotide, our drug candidate for the treatment for obesity and related metabolic disorders. Approximately seven of these patents are United States patents and the remaining patents are validated in Belgium, Switzerland, Germany, Spain, France, Japan, the United Kingdom, Ireland, Greece, Italy, Netherlands, Portugal, Sweden and Turkey.

Patent Group	Estimated Year of Expiration
Adipotide®	
Targeting moieties and conjugates	2021
Targeted Pharmaceutical Compositions	2021
Homing Peptides	
EphA5 Targeting Peptides	2027
IL-11R Targeting Peptides	2022





## Non-Exclusively Licensed Patent Rights obtained from Roche

Roche and the Company entered into a Stock and Asset Purchase Agreement on October 21, 2011 pursuant to which Roche assigned to Arrowhead its entire rights under certain licenses including: the License and Collaboration Agreement between Roche and Alnylam dated July 8, 2007 (the “Alnylam License”); the Non-Exclusive Patent License Agreement between Roche and MDRNA, Inc. dated February 12, 2009 (“MDRNA License”); and the Non-Exclusive License Agreement between Roche and City of Hope dated September 19, 2011 (the “COH License”) (Collectively the “RNAi Licenses”). The RNAi Licenses provide the Company with non-exclusive, worldwide, perpetual, irrevocable, royalty-bearing rights and the right to sublicense a broad portfolio of intellectual property relating to the discovery, development, manufacture, characterization, and use of therapeutic products that function through the mechanism of RNA interference for specified targets.

### Terms of the Alnylam License

The Alnylam License provides us with a non-exclusive, worldwide, perpetual, irrevocable, royalty-bearing right and sublicenseable license under Alnylam’s rights in certain intellectual property existing as of its effective date, to engage in discovery, development, commercialization and manufacturing activities, including to make, have made, use, offer for sale, sell and import certain licensed products in certain fields. The fields include the treatment or prophylaxis of indications comprising an RNAi compound complementary to, and function in mediating the RNAi of, a target known or believed to be primarily implicated in one or more primary therapeutic areas. The primary therapeutic areas are cancer, hepatic, metabolic disease and pulmonary disease. The hepatic therapeutic area specifically excludes targets of infectious pathogen.

The Alnylam license excludes access to intellectual property specifically related to “Blocked Targets.” “Blocked Targets” are those targets that are subject to a contractual obligation of a pre-existing agreement between Alnylam and its alliance partners.

Under the Alnylam License, we may be obligated to pay development and sales milestone payments of up to the mid to upper double digit millions of dollars for each licensed product that progresses through clinical trials in a particular indication, receives marketing approval for that indication and is the subject of a first commercial sale. Additionally, we may be obligated to pay mid to high single digit percentage royalties on sales of such products.

### Core Patents relating to RNAi

The RNAi Licenses include patents relating to the general structure, architecture, and design of double-stranded oligonucleotide molecules, which engage RNA interference mechanisms in a cell. These rights include the “Tuschl II” patents, including issued U.S. Patent Nos. 7,056,704; 7,078,196; 7,078,196; 8,329,463; 8,362,231; 8,372,968; and 8,445,327; “Tuschl I” patents, including U.S. Patent Nos. 8,394,628 and 8,420,391; and allowed “Tuschl I” patent application, U.S. Publication No. 2011024446; “City of Hope” patents, including U.S. Patent No. 8,084,599; and “Kreutzer-Limmer” patents assigned to Alnylam, including U.S. Patent Nos. 7,829,693; 8,101,594; 8,119,608; 8,202,980; and 8,168,776.

Thomas Tuschl is the first named inventor on “Tuschl I” and “Tuschl II.” “Tuschl I” refers to the patents arising from the patent application entitled “The Uses of 21-23 Sequence-Specific Mediators of Double-Stranded RNA Interference as a Tool to Study Gene Function and as a Gene-Specific Therapeutic.” “Tuschl II” patents refer to the patents and patent applications arising from the patent application entitled “RNA Interference Mediating Small RNA Molecules.” “City of Hope” is the first named assignee of certain core RNAi trigger patents. The second named assignee of these patents is Integrated DNA Technologies, Inc. Kreutzer-Limmer patents refer to the Alnylam patents and patent applications, relating to core siRNA IP, which includes inventors, Roland Kreutzer and Stefan Limmer.

### Chemical modifications of double-stranded oligonucleotides

The RNAi Licenses also include patents related to modifications of double-stranded oligonucleotides, including modifications to the base, sugar, or internucleoside linkage, nucleotide mimetics, and end modifications, which do not abolish the RNAi activity of the double-stranded oligonucleotides. Also included are patents relating to modified double-stranded oligonucleotides, such as meroduplexes described in U.S. Publication No. 20100209487 assigned to Marina Biotech (f/k/a MDRNA, Inc.), and microRNAs described in U.S. Patent Nos. 7,582,744; 7,674,778, and 7,772,387 assigned to Alnylam as well as U.S. Patent No. 8,314,227 related to unlocked nucleic acids (UNA). The '227 patent was assigned by Marina Biotech to Arcturus Therapeutics, Inc. but remains part of the MDRNA License. The RNAi Licenses also include rights from INEX/Tekmira relating to lipid-nucleic acid particles, and oligonucleotide modifications to improve pharmacokinetic activity including resistance to degradation, increased stability, and more specific targeting of cells from Alnylam and ISIS Pharmaceuticals, Inc.

#### Manufacturing techniques for the double-stranded oligonucleotide molecules or chemical modifications

The RNAi Licenses also include patents relating to the synthesis and manufacture of double-stranded oligonucleotide molecules for use in RNA interference, as well as chemical modifications of such molecules, as described above. These include methods of synthesizing the double-stranded oligonucleotide molecules such as in the core “Tuschl I” allowed U.S. Application No. 12/897,749, the core “Tuschl II” U.S. Patent Nos. 7,056,704; 7,078,196; and 8,445,327; and Alnylam’s U.S. Patent Nos. 8,168,776, as well as methods of making chemical modifications of the double-stranded oligonucleotides such as described in Alnylam’s U.S. Patent No. 7,723,509 and INEX’s U.S. Patent Nos. 5,976,567; 6,858,224; and 8,484,282. Patent applications are currently pending that further cover manufacturing techniques for double-stranded oligonucleotide molecules or chemical modifications.

#### Uses and Applications of Double-Stranded Oligonucleotide Molecules or Chemical modifications

The RNAi Licenses also include patents related to uses of the double-stranded oligonucleotides that function through the mechanism of RNA interference. These include for example, the core “Tuschl I” U.S. Patent No. 8,394,628 and “Tuschl II” U.S. Patent No. 8,329,463; Alnylam’s U.S. Patent Nos. 7,763,590; 8,101,594, and 8,119,608, and City of Hope’s U.S. Patent No. 8,084,599. Other more specific uses have been acquired and patent applications are currently pending that cover additional end uses and applications of double-stranded oligonucleotides functioning through RNA interference.

#### License from Alnylam

In January 2012, we obtained a license from Alnylam under its rights in certain RNAi intellectual property to develop and commercialize RNAi-based products targeting RNAs encoded by the genome of HBV.

Alnylam granted us a worldwide non-exclusive sublicensable royalty bearing license under Alnylam’s general RNAi intellectual property estate to research, develop and commercialize RNAi-based products targeting HBV RNAs in combination with DPC™ technology. Alnylam further granted us a worldwide sublicensable exclusive royalty bearing license under its target-specific RNAi patent rights to research, develop and commercialize RNAi-based products targeting HBV RNAs in combination with DPC™ technology. Alnylam further agreed to forego the development of any RNAi-based products targeting HBV RNAs in combination with DPC™ technology.

Under the license from Alnylam, we may be obligated to pay development and sales milestone payments of up to the low double digit millions of dollars for each licensed product that progresses through clinical trials, receives marketing approval and is the subject of a first commercial sale. Additionally, we may be obligated to pay low single digit percentage royalties on sales of such products.

#### License to Alnylam

In consideration for the licenses from Alnylam, in January 2012 we granted Alnylam a worldwide non-exclusive, sublicensable royalty bearing license under our broad and target-specific DPC™ intellectual property rights to research, develop and commercialize RNAi-based products against a single undisclosed target in combination with DPC™ technology. Under the license to Alnylam, Alnylam may be obligated to pay us development and sales milestone payments of up to the low double digit millions of dollars for each licensed product that progresses through clinical trials, receives marketing approval and is the subject of a first commercial sale. Additionally, Alnylam may be obligated to pay us low single digit percentage royalties on sales of such products.

#### University of Texas MD Anderson Cancer Center License

In December 2010, we obtained an exclusive worldwide license from the University of Texas MD Anderson Cancer Center in Houston, Texas (“UTMDACC”) related to Adipotide technology (the “UTMDACC License”). The UTMDACC

License granted us a royalty-bearing, exclusive right (with the right to sublicense) under certain UTMDACC patents to develop and commercialize certain products in the fields of: 1) therapeutics, diagnostics and research services that both (i) incorporate peptides that specifically target adipose tissue, and (ii) are used to treat, diagnose or research solely either (a) obesity, overweight and/or (b) metabolic conditions related to, caused by and/or associated with obesity and overweight, e.g., diabetes; and 2) cancer therapies, diagnostics and research products associated with a specific targeting moiety. We also have rights to certain improvements to the technology.

In consideration for the license, we paid UTMDACC an upfront fee of \$2 million and are obligated to pay annual fees initially equal to \$50,000 increasing up to a maximum of \$100,000, with such annual fees creditable against milestone payments.

We may be obligated to pay development milestone payments of up to \$8.3 million for each UTMDACC licensed product that progresses through clinical trials and receives U.S. marketing approval. Additional EU and Japanese approval milestone payments are in the low single digit million dollar range. If a commercial drug is developed and approved, royalty payments on net sales of UTMDACC licensed products are in the low single digit range. If we sublicense or partner a UTMDACC licensed product,

UTMDACC would receive partnering fee percentages in the range of single digits to the twenties, depending on the stage of development of the partnered UTMDACC licensed product.

The term of the UTMDACC License is linked to the last to expire patents licensed therein or 15 years if a licensed product contains only licensed know-how. We are obligated to actively and effectively attempt to commercialize the UTMDACC Technology and submit to UTMDACC a Phase 2 clinical trial protocol within two years of obtaining an approved IND. We are also obligated to commence a Phase 2 clinical trial within four years and a Phase 3 clinical trial within seven years of approval of an IND. However, we may obtain yearly extensions of time upon the payment of an increasing fee in the range of tens of thousands of dollars up to several hundred thousand dollars. We also have diligence obligations with respect to any UTMDACC Improvements later added to the license.

#### Acquisition of Assets from Novartis

On March 3, 2015, the Company entered into an Asset Purchase and Exclusive License Agreement (the “RNAi Purchase Agreement”) with Novartis pursuant to which the Company acquired Novartis’ RNAi assets and rights thereunder. Pursuant to the RNAi Purchase Agreement, the Company acquired or licensed certain patents and patent applications owned or controlled by Novartis related to RNAi therapeutics, assignment of Novartis’s rights under a license from Alnylam (the “Alnylam-Novartis License”), rights to three pre-clinical RNAi candidates, and a license to certain Novartis assets (the “Licensed Novartis Assets”). The patents acquired from Novartis include multiple patent families covering delivery technologies and RNAi-trigger design rules and modifications. The Licensed Novartis Assets include an exclusive, worldwide right and license, solely in the RNAi field, with the right to grant sublicenses through multiple tiers under or with respect to certain patent rights and know how relating to delivery technologies and RNAi-trigger design rules and modifications. Under the assigned Alnylam-Novartis License, the Company has acquired a worldwide, royalty-bearing, exclusive license with limited sublicensing rights to existing and future Alnylam intellectual property (coming under Alnylam’s control on or before March 31, 2016), excluding intellectual property concerning delivery technology, to research, develop and commercialize 30 undisclosed gene targets.

#### Research and Development

##### Research and Development Facility

Arrowhead’s research and development operations are located in Madison, Wisconsin and are housed in two facilities. The main facility was built and equipped by Roche and was part of our 2011 acquisition of Roche’s RNA therapeutics business. A second research and development facility, located in a nearby Madison suburb, was opened in 2015 as operations expanded. Substantially all of the Company’s assets are located either in these facilities or in our corporate headquarters in Pasadena. A summary of our research and development facilities is provided below:

- Approximately 87 scientists;
- State-of-the-art laboratories in two buildings: main building has 27,000 total sq. ft. (16,000 sq. ft. lab, 11,000 sq. ft. office); second building has 2,900 total sq. ft. (1,700 sq. ft. lab, 1,200 sq. ft. office);
- Complete small animal facility;
- Primate colony housed at the Wisconsin National Primate Research Center, an affiliate of the University of Wisconsin;
- In-house histopathology capabilities;
- Animal models for metabolic, viral, and oncologic diseases;
- Animal efficacy and safety assessment;
- Polymer, peptide, oligonucleotide and small molecule synthesis and analytics capabilities (HPLC, NMR, MS, etc.);
- Polymer, peptide and oligonucleotide PK, biodistribution, clearance methodologies; and
- Conventional and confocal microscopy, flow cytometry, Luminex platform, qRT-PCR, clinical chemistry analytics.

##### Research and Development Expenses

Research and development (R&D) expenses consist of costs incurred in discovering, developing and testing our clinical candidates and platform technologies. R&D expenses also include costs related to clinical trials, including costs of contract research organizations to recruit patients and manage clinical trials. Other costs associated with clinical trials include manufacturing of clinical supplies, as well as good laboratory practice (“GLP”) toxicology studies necessary to support clinical trials, both of which are

outsourced to cGMP-compliant manufacturers and GLP-compliant laboratories. Total research and development expense for fiscal 2015 was \$47.3 million, an increase from \$23.1 million in 2014 and \$8.7 million in 2013.

We employ approximately 87 employees in an R&D function, primarily working from our facility in Madison, Wisconsin. These employees are engaged in various areas of research on Arrowhead candidate and platform development including synthesis and analytics, PK/biodistribution, formulation, CMC and analytics, tumor and extra-hepatic targeting, bioassays, live animal research, toxicology/histopathology, clinical and regulatory operations, and other areas. Salaries and payroll-related expenses for our R&D activities were \$11.6 million in fiscal 2015, \$7.8 million in fiscal 2014, and \$4.1 million in fiscal 2013. Laboratory supplies including animal-related costs for in-vivo studies were \$3.1 million, \$2.3 million, and \$1.3 million in fiscal 2015, 2014, and 2013, respectively.

Costs related to manufacture of clinical supplies, GLP toxicology studies and other outsourced lab studies, as well as clinical trial costs were \$41.8 million, \$18.8 million, and \$6.1 million in fiscal 2015, 2014, and 2013 respectively.

Facility-related costs, primarily rental costs for our leased laboratory in Madison, Wisconsin were \$1.0 million, \$0.9 million, and \$0.7 million in fiscal 2015, 2014, and 2013, respectively. Other research and development expenses were \$1.4 million, \$1.2 million, and \$0.6 million in fiscal 2015, 2014 and 2013, respectively. These expenses are primarily related to milestone payments, which can vary from period to period depending on the nature of our various license agreements, and the timing of reaching various development milestones requiring payment.

#### Government Regulation

Government authorities in the United States, at the federal state, and local levels, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, product approval, manufacture, quality control, manufacturing changes, packaging, storage, recordkeeping, labeling, promotion, advertising, sales, distribution, marketing, and import and export of drugs and biologic products. All of our foreseeable product candidates are expected to be regulated as drugs. The processes for obtaining regulatory approval in the U.S. and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities both pre- and post-commercialization, are a significant factor in the production and marketing of our products and our R&D activities and require the expenditure of substantial time and financial resources.

#### Review and Approval of Drugs in the United States

In the U.S., the FDA and other government entities regulate drugs under the Federal Food, Drug, and Cosmetic Act (the "FDCA"), the Public Health Service Act, and the regulations promulgated under those statutes, as well as other federal and state statutes and regulations. Failure to comply with applicable legal and regulatory requirements in the U.S. at any time during the product development process, approval process, or after approval, may subject us to a variety of administrative or judicial sanctions, such as a delay in approving or refusal by the FDA to approve pending applications, withdrawal of approvals, delay or suspension of clinical trials, issuance of warning letters and other types of regulatory letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil monetary penalties, refusals of or debarment from government contracts, exclusion from the federal healthcare programs, restitution, disgorgement of profits, civil or criminal investigations by the FDA, U.S. Department of Justice, State Attorneys General, and/or other agencies, False Claims Act suits and/or other litigation, and/or criminal prosecutions.

An applicant seeking approval to market and distribute a new drug in the U.S. must typically undertake the following:

(1) completion of pre-clinical laboratory tests, animal studies, and formulation studies in compliance with the FDA's GLP regulations;

(2) submission to the FDA of an Investigational New Drug Application (“IND”) for human clinical testing, which must become effective without FDA objection before human clinical trials may begin;

(3) approval by an independent institutional review board (“IRB”), representing each clinical site before each clinical trial may be initiated;

(4) performance of adequate and well-controlled human clinical trials in accordance with the FDA’s current good clinical practice (“cGCP”) regulations, to establish the safety and effectiveness of the proposed drug product for each indication for which approval is sought;

(5) preparation and submission to the FDA of a New Drug Application (“NDA”);

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- (6) satisfactory review of the NDA by an FDA advisory committee, where appropriate or if applicable,
- (7) satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the drug product, and the active pharmaceutical ingredient or ingredients thereof, are produced to assess compliance with current good manufacturing practice (“cGMP”) regulations and to assure that the facilities, methods, and controls are adequate to ensure the product’s identity, strength, quality, and purity;
- (8) payment of user fees, as applicable, and securing FDA approval of the NDA; and
- (9) compliance with any post-approval requirements, such as any Risk Evaluation and Mitigation Strategies (“REMS”) or post-approval studies required by the FDA.

#### Preclinical Studies and an IND

Preclinical studies can include in vitro and animal studies to assess the potential for adverse events and, in some cases, to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. Other studies include laboratory evaluation of the purity, stability and physical form of the manufactured drug substance or active pharmaceutical ingredient and the physical properties, stability and reproducibility of the formulated drug or drug product. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, to the FDA as part of an IND. Some preclinical testing, such as longer-term toxicity testing, animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Following commencement of a clinical trial under an IND, the FDA may place a clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

#### Human Clinical Studies in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with cGCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the NIH for public dissemination on its ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

Phase 1: The product candidate is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.

Phase 2: The product candidate is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3: The product candidate is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for

approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2, and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites in late-stage clinical trials to assure compliance with cGCP and the integrity of the clinical data submitted.

#### Submission of an NDA to the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to an application user fee, currently exceeding \$2.3 million for fiscal year 2016, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding \$114,450 per product and \$585,200 per establishment for fiscal year 2016. These fees are typically increased annually.

Under certain circumstances, the FDA will waive the application fee for the first human drug application that a small business, defined as a company with less than 500 employees, or its affiliate, submits for review. An affiliate is defined as a business entity that has a relationship with a second business entity if one business entity controls, or has the power to control, the other business entity, or a third party controls, or has the power to control, both entities. In addition, an application to market a prescription drug product that has received orphan designation is not subject to a prescription drug user fee unless the application includes an indication for other than the rare disease or condition for which the drug was designated.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with cGCP.

The FDA also may require submission of an REMS plan to mitigate any identified or suspected serious risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

## The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

The product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety and effectiveness of drug products.

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the U.S. and for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for this type of disease or condition will be recovered from sales in the U.S. for that drug. Orphan drug designation must be requested before submitting an NDA, and both the drug and the disease or condition must meet certain criteria specified in the Orphan Drug Act and FDA's implementing regulations at 21 C.F.R. Part 316. The granting of an orphan drug designation does not alter the standard regulatory requirements and process for obtaining marketing approval. Safety and effectiveness of a drug must be established through adequate and well-controlled studies.

After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other application to market the same drug for the same indication, except in very limited circumstances, for seven years.

## Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior

FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events or problems with manufacturing processes of unanticipated severity or frequency, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
  - product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act (PDMA), which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

#### Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the “Hatch-Waxman Amendments”) amending the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application (ANDA) to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD. To reference that information, however, the ANDA applicant must demonstrate, and the FDA must conclude, that the generic drug does, in fact, perform in the same way as the RLD it purports to copy. Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug.

At the same time, the FDA must also determine that the generic drug is “bioequivalent” to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if “the rate and extent of absorption of the generic drug do not show a significant difference from the rate and extent of absorption of the RLD.” Upon approval of an ANDA, the FDA indicates that the generic product is “therapeutically equivalent” to the RLD and it assigns a therapeutic equivalence rating to the approved generic drug in its publication “Approved Drug Products with Therapeutic Equivalence Evaluations,” also referred to as the “Orange Book.” Physicians and pharmacists consider the therapeutic equivalence rating to mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA’s designation of a therapeutic equivalence rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of nonpatent exclusivity for the RLD has expired. The FDCA provides a period of five years of data exclusivity for new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.



### Hatch-Waxman Patent Certification and the 30 Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

To the extent that a Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

### Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act, or FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot accept or approve another application.

## Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Amendments. Those Amendments permit a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of a NDA, plus the time between the submission date of a NDA and ultimate approval. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

## Review and Approval of Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of a European Union member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial applications must be accompanied by an investigational medicinal product dossier with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

To obtain marketing approval of a drug under European Union regulatory systems, an applicant must submit a marketing authorization application (MAA) either under a centralized or decentralized procedure.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use (CHMP) established at the European Medicines Agency (EMA) is responsible for conducting the initial assessment of a drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated

evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various European Union member states where such product has not received marketing approval in any European Union member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

#### Data and Market Exclusivity in the European Union

In the European Union, new chemical entities qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the sponsor is able to gain the prescribed period of data exclusivity, another company nevertheless could also market another version of the drug if such company can complete a full MAA with a complete database of pharmaceutical test, preclinical tests and clinical trials and obtain marketing approval of its product.

#### Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs such as, in the United States, Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. A payor's decision to provide coverage for a drug product does not necessarily imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on our investment in product development.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. Third-party payors are increasingly challenging the prices charged for medical products and services and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider a product to be cost effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, risk sharing, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals. As a result, the marketability of any product which receives regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement.

In addition, an increasing emphasis on managed care in the United States has increased and will continue to increase the pressure on drug pricing. Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. In particular, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Even if favorable coverage and reimbursement status is attained for one or more products that receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements for any of our products.

### Healthcare Laws and Regulation

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal healthcare Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal Foreign Corrupt Practices Act (FCPA) prohibits, among other things, U.S. corporations and their persons acting on their behalf from offering, promising, authorizing or making payments to any foreign government official, including certain healthcare professionals in many countries, in an attempt to obtain or retain business or otherwise seek preferential treatment abroad;
- the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent, making a false statement material to a false or fraudulent claim, or improperly avoiding, decreasing, or concealing an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA) imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the federal Physician Payment Sunshine Act requires manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by nongovernmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

#### Certain Financial Information

The financial information required in this Item 1 is included in Part II, Item 6 and Part IV, Item 15 of this Annual Report Form 10-K.

33

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## Corporate Information

Arrowhead was originally incorporated in South Dakota in 1989, and was reincorporated in Delaware in 2000. The Company's principal executive offices are located at 225 South Lake Avenue, Suite 1050, Pasadena, California 91101, and its telephone number is (626) 304-3400. We also operate a research and development facility in Madison, Wisconsin. As of September 30, 2015, Arrowhead had 104 full-time employees.

## Investor Information

Our internet website address is <http://www.arrowheadresearch.com>. Our reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, including our annual reports on Form 10-K, our quarterly reports on Form 10-Q and our current reports on Form 8-K, and amendments to those reports, are accessible through our website, free of charge, as soon as reasonably practicable after these reports are filed electronically with, or otherwise furnished to, the SEC. These SEC reports can be accessed through the "Investors" section of our website.

You may read and copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet website that contains reports, proxy and information statements, and other information regarding Arrowhead and other issuers that file electronically with the SEC. The SEC's Internet website address is <http://www.sec.gov>.

## ITEM 1A. RISK FACTORS

You should carefully consider the risks discussed below and all of the other information contained in this report in evaluating us and an investment in our securities. If any of the following risks and uncertainties should occur, they could have a material adverse effect on our business, financial condition or results of operations. In that case, the trading price of our Common Stock could decline. Additionally, we note that we have accrued net losses annually since inception given the stage of our drug development. We urge you to consider our likelihood of success and prospects in light of the risks, expenses and difficulties frequently encountered by entities at similar stages of development.

### Risks Related to Our Company

Drug development is time consuming, expensive and risky.

We are focused on technology related to new and improved pharmaceutical candidates. Product candidates that appear promising in the early phases of development, such as in animal and early human clinical trials, often fail to reach the market for a number of reasons, such as:

Clinical trial results may be unacceptable, even though preclinical trial results were promising;

Inefficacy and/or harmful side effects in humans or animals;

The necessary regulatory bodies, such as the U.S. Food and Drug Administration, may not approve our potential product for the intended use, or at all; and

Manufacturing and distribution may be uneconomical.

For example, the positive pre-clinical results in animals for ARC-520, ARC-AAT, and our other programs may not be replicated in human clinical studies. These programs may be also found to be unsafe in humans, particularly at higher doses needed to achieve the desired levels of efficacy. Also, the positive safety results for ARC-520 from single dose human clinical studies may not be replicated in other human studies, including multiple dose studies. Clinical trial results are frequently susceptible to varying interpretations by scientists, medical personnel, regulatory personnel, statisticians and others, which often delays, limits, or prevents further clinical development or regulatory approvals of potential products. Clinical trials can take many years to complete, including the process of study design, clinical site selection and the recruitment of patients. As a result, we can experience significant delays in completing clinical studies, which can increase the cost of developing a drug candidate and shorten the time that an approved product may be protected by patents. If our drug candidates are not successful in human clinical trials, we may be forced to curtail or abandon certain development programs. If we experience significant delays in commencing or completing our clinical studies, we could suffer from significant cost overruns, which could negatively affect our capital resources and our ability to complete these studies.

There are substantial risks inherent in attempting to commercialize new drugs, and, as a result, we may not be able to successfully develop products for commercial use.

Our research and development efforts involve therapeutics based on RNA interference and our delivery systems, which are largely unproven technologies. Our scientists and engineers are working on developing technology in the early stages. However, such technology's commercial feasibility and acceptance are unknown. Scientific research and development requires significant amounts of capital and takes a long time to reach commercial viability, if it can be

achieved at all. To date, our research and development projects have not produced commercially viable drugs, and may never do so. During the research and development process, we may experience technological barriers that we may be unable to overcome. Further, certain underlying premises in our development programs, including ARC-520, are not proven. For instance, the theory that knockdown of S-antigen in chronic hepatitis B patients will result in a functional cure is unproven. Thus, even if ARC-520 is successful at reducing S-antigen levels in patients, it may not be a commercially viable drug if there is not a corresponding medical benefit related to the underlying Hepatitis B infection. Similarly, if ARC-AAT successfully reduces the production of mutant alpha-1 antitrypsin in the liver, it may not lead to a reduction of globules in the liver, and even if it leads to a reduction in such globules, this may not lead to other beneficial hepatic changes. It is also unknown at this time what changes in the liver may be required to gain regulatory approval and/or favorable reimbursement,. Because of these and similar uncertainties, it is possible that no commercial products will be successfully developed. If we are unable to successfully develop commercial products, we will be unable to generate revenue or build a sustainable or profitable business.

Our drug candidates are in the early stages of development and because we have a short development history with both RNA interference and our delivery technologies, there is a limited amount of information about us upon which you can evaluate our business and prospects.

We have no approved drugs and thus have not begun to market or generate revenues from the commercialization of any products. We have only a limited history upon which one can evaluate our RNAi therapeutic business as our drug candidates are still at an early stage of development. Thus, we have limited experience and have not yet demonstrated an ability to successfully overcome

many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

Execute product development activities using unproven technologies;

Build, maintain and protect a strong intellectual property portfolio;

Demonstrate safety and efficacy of our drug candidates in multiple human clinical studies;

Receive FDA approval and approval from similar foreign regulatory bodies;

Gain market acceptance for the development and commercialization of any drugs we develop;

Ensure our products are reimbursed by commercial and/or government payors at a rate that permits commercial viability;

Develop and maintain successful strategic relationships with suppliers, distributors, and commercial licensing partners; and

Manage our spending and cash requirements as our expenses will increase in the near term if we add programs and additional preclinical and clinical trials.

If we are unsuccessful in accomplishing these objectives, we may not be able to develop products, raise capital, expand our business or continue our operations.

We may be unable to attract revenue-generating collaborations with other pharmaceutical and biotech companies to advance our drug candidates.

Our business strategy includes obtaining collaborations with other pharmaceutical and biotech companies to support the development of our therapeutic siRNA and other drug candidates. We may not be able to attract such partners, and even if we are able to enter into such partnerships, the terms may be less favorable than anticipated. Further, entering into partnership agreements may limit our commercialization options and/or require us to share revenues and profits with our partners. If we are unable to enter into any of these agreements on commercially attractive terms, we may be unable to develop certain programs due to a limited availability of resources, and we may need to raise additional capital, which could be dilutive to our existing investors.

We will need to achieve commercial acceptance of our drug candidates to generate revenues and achieve profitability.

Even if our research and development efforts yield technologically feasible applications, we may not successfully develop commercial products. Drug development takes years of study in human clinical trials prior to regulatory approval, and, even if we are successful, it may not be on a timely basis. During our drug development period, superior competitive technologies may be introduced which could diminish or extinguish the potential commercial uses for our drug candidates. Additionally, the degree to which the medical community and consumers will adopt any product we develop is uncertain. The rate and degree of market acceptance of our products will depend on a number of factors, including the establishment and demonstration in the medical community of the clinical efficacy and safety of our products, their potential advantage over alternative treatments, and the costs to patients and third-party payors, including insurance companies and Medicare. Recent efforts in the United States and abroad to reduce overall healthcare spending has put significant pressure on the price of prescription drugs and certain companies have been publicly criticized for the relatively high cost of their therapies. These pressures may force us to sell any approved

drugs at a lower price than we or analysts may anticipate, or may result in lower levels of reimbursement and coverage from third parties.

We cannot predict whether significant commercial market acceptance for our products, if approved, will ever develop, and we cannot reliably estimate the projected size of any such potential market. Our revenue growth and achievement of profitability will depend substantially on our ability to introduce products that will be accepted by the medical community. If we are unable to cost-effectively achieve acceptance of our technology among the medical establishment and patients, or if the associated products do not achieve wide market acceptance, our business will be materially and adversely affected.

#### Risks Related to Our Financial Condition

We have a history of net losses, and we expect to continue to incur net losses and may not achieve or maintain profitability.

We have incurred net losses since our inception, including net losses of \$91.9 million for the year ended September 30, 2015. We expect that our operating losses will continue for the foreseeable future as we continue our drug development and discovery efforts. To achieve profitability, we must, either directly or through licensing and/or partnering relationships, meet certain milestones, successfully develop and obtain regulatory approval for one or more drug candidates and effectively manufacture, market and sell any drugs we successfully develop. Even if we successfully commercialize drug candidates that receive regulatory approval, we may not be able to realize revenues at a level that would allow us to achieve or sustain profitability.

Accordingly, we may never generate significant revenue and, even if we do generate significant revenue, we may never achieve profitability.

We will require substantial additional funds to complete our research and development activities.

Our business currently does not generate the cash that is necessary to finance our operations. Subject to the success of the research and development programs of our company and our partners, and potential licensing or partnering transactions, we will likely need to raise additional capital to:

Fund research and development infrastructure and activities relating to the development of our drug candidates, including pre-clinical and clinical trials and manufacturing to support these efforts;

Fund our general and administrative infrastructure and activities;

Pursue business development opportunities for our technologies;

Add to and protect our intellectual property; and

Retain our management and technical staff.

Our future capital needs depend on many factors, including:

- The scope, duration and expenditures associated with our research and development;
- Regulatory requirements for our clinical trials;
- The extent to which our R&D and clinical efforts are successful;
- The outcome of potential partnering or licensing transactions, if any, and the extent to which our business development efforts result in the acquisition of new programs or technologies;
- Competing technological developments;
- Our intellectual property positions, if any, in our products; and
- The regulatory approval process and regulatory standards for our drug candidates.

We will need to raise additional funds through public or private equity offerings, debt financings or additional strategic alliances and licensing arrangements in the future to continue our operations. We may not be able to obtain additional financing on terms favorable to us, if at all. General market conditions may make it very difficult for us to seek financing from the capital markets, and the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our stockholders will result, which may substantially dilute the value of your investment. In addition, as a condition to

providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets. In order to raise additional funds through alliance, joint venture or licensing arrangements, we may be required to relinquish rights to our technologies or drug candidates, or grant licenses on terms that are not favorable to us. If adequate funds are not available, we may have to further delay, reduce or eliminate one or more of our planned activities. These actions would likely reduce the market price of our common stock.

If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements prove inaccurate, our actual results may vary from those reflected in our accruals.

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America (GAAP). The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges accrued by us and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct.

The investment of our cash, cash equivalents and fixed income marketable securities is subject to risks which may cause losses and affect the liquidity of these investments.

At September 30, 2015, we had \$17.5 million in fixed income marketable securities. These investments are in corporate bonds nearing maturity, but our investments may also include commercial paper, securities issued by the U.S. government obligations, certificates of deposit and money market funds meeting the criteria of our investment policy, which is focused on the preservation of

our capital. These investments are subject to general credit, liquidity, and market and interest rate risks, particularly in the current economic environment. We may realize losses in the fair value of these investments or a complete loss of these investments, which would have a negative effect on our consolidated financial statements. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. The market risks associated with our investment portfolio may have an adverse effect on our results of operations, liquidity and financial condition.

We may not be able to effectively secure first-tier technologies when competing against other companies or investors.

Our future success may require that we acquire patent rights and know-how to new or complimentary technologies. However, we compete with a substantial number of other companies that may also compete for technologies we desire. In addition, many venture capital firms and other institutional investors, as well as other pharmaceutical and biotech companies, invest in companies seeking to commercialize various types of emerging technologies. Many of these companies have greater financial, scientific and commercial resources than us. Therefore, we may not be able to secure the technologies we desire. Furthermore, should any commercial undertaking by us prove to be successful, there can be no assurance competitors with greater financial resources will not offer competitive products and/or technologies.

#### Risks Associated with Reliance on Third Parties

We will need to establish additional relationships with strategic and development partners to fully develop our drug candidates and market any approved products.

We do not possess all of the financial and development resources necessary to develop and commercialize products that may result from our technologies. Unless we expand our product development capacity and enhance our internal marketing capability, we may need to make appropriate arrangements with strategic partners to develop and commercialize any drug candidates that may be approved. If we do not find appropriate partners, or if our existing arrangements or future agreements are not successful, our ability to develop and commercialize products could be adversely affected. Even if we are able to find collaborative partners, the overall success of the development and commercialization of product candidates in those programs will depend largely on the efforts of other parties and will be beyond our control. In addition, in the event we pursue our commercialization strategy through collaboration or licenses to third parties, there are a variety of technical, business and legal risks, including:

We may not be able to control the amount and timing of resources that our collaborators may be willing or able to devote to the development or commercialization of our drug candidates or to their marketing and distribution; and

Disputes may arise between us and our collaborators that result in the delay or termination of the research, development or commercialization of our drug candidates or that result in costly litigation or arbitration that diverts our management's resources.

The occurrence of any of the above events or other related events could impair our ability to generate revenues and harm our business and financial condition.

We may lose a considerable amount of control over our intellectual property and may not receive anticipated revenues in strategic transactions, particularly where the consideration is contingent on the achievement of development or sales milestones.

Our business model has been to develop new technologies and to utilize the intellectual property created through the research and development process to develop commercially successful products. If the acquirers of our technologies



fail to achieve performance milestones, we may not receive a significant portion of the total value of any sale, license or other strategic transaction.

We rely on outside sources for various components and processes for our products.

We rely on third parties for various components and processes for our product candidates. We may not be able to achieve multiple sourcing because there may be no acceptable second source, other companies may choose not to work with us, or the component or process sought may be so new that a second source does not exist, or does not exist on acceptable terms. There may be a disruption or delay in the performance of our third-party contractors, suppliers or collaborators which is beyond our control. If such third parties are unable to satisfy their commitments to us, the development of our products would be adversely affected. Therefore, it is possible that our development plans will have to be slowed down or stopped completely at times due to our inability to obtain required raw materials, components and outsourced processes at an acceptable cost, if at all, or to get a timely response from vendors.

We have limited manufacturing capability and must rely on third-party manufacturers to manufacture our clinical supplies and commercial products, if and when approved, and if they fail to meet their obligations, the development and commercialization of our products could be adversely affected.

We have limited manufacturing capabilities and experience. ARC-520 and our other drug candidates are composed of multiple components and require specialized formulations for which scale-up and manufacturing could be difficult. We have limited experience

in such scale-up and manufacturing requiring us to depend on a limited number of third parties, who may not be able to deliver in a timely manner, or at all. In order to develop products, apply for regulatory approvals and commercialize our products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. Our internal manufacturing capabilities are limited to small-scale production of material for use in in vitro and in vivo experiments that is not required to be produced under cGMP standards. There are a limited number of manufacturers that supply synthetic siRNAs. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our contract manufacturers to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are synthesis and purification failures and contamination during the manufacturing process, which could result in unusable product and cause delays in our development process, as well as additional expense to us.

Additionally, our product candidates have not yet been manufactured for commercial use. If any of our product candidates become approved for commercial sale, we will need to establish third-party manufacturing capacity. A third-party manufacturing partner may require us to fund capital improvements to support the scale-up of manufacturing and related activities. The third-party manufacturer may not be able to establish scaled manufacturing capacity for an approved product in a timely or economic manner, if at all. If a manufacturer is unable to provide commercial quantities of such an approved product, we will have to successfully transfer manufacturing technology to a different manufacturer. Engaging a new manufacturer for such an approved product could require us to conduct comparative studies or utilize other means to determine bioequivalence of the new and prior manufacturers' products, which could delay or prevent our ability to commercialize such an approved product. If any of these manufacturers is unable or unwilling to increase its manufacturing capacity or if we are unable to establish alternative arrangements on a timely basis or on acceptable terms, the development and commercialization of such an approved product may be delayed or there may be a shortage in supply. Any inability to manufacture our product candidates or future approved drugs in sufficient quantities when needed would seriously harm our business.

Manufacturers of our approved products, if any, must comply with cGMP requirements enforced by the FDA and foreign health authorities through facilities inspection programs. These requirements include quality control, quality assurance, and the maintenance of records and documentation. Manufacturers of our approved products, if any, may be unable to comply with these cGMP requirements and with other FDA, state, and foreign regulatory requirements. We have little control over our manufacturers' compliance with these regulations and standards. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval. If the safety of any quantities supplied is compromised due to our manufacturer's failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our products, which would seriously harm our business.

We rely on third parties to conduct our clinical trials, and if they fail to fulfill their obligations, our development plans may be adversely affected.

We rely on independent clinical investigators, contract research organizations and other third-party service providers to assist us in managing, monitoring and otherwise carrying out our clinical trials. We have contracted with, and we plan to continue to contract with, certain third-parties to provide certain services, including site selection, enrollment, monitoring and data management services. Although we depend heavily on these parties, we do not control them and therefore, we cannot be assured that these third-parties will adequately perform all of their contractual obligations to us. If our third-party service providers cannot adequately and timely fulfill their obligations to us, or if the quality and accuracy of our clinical trial data is compromised due to failure by such third-parties to adhere to our protocols or regulatory requirements or if such third-parties otherwise fail to meet deadlines, our development plans may be delayed or terminated. Further, if clinical study results are compromised, then we may need to repeat the affected studies, which could result in significant additional costs and delays to us.

Risks related to managing our operations

Our success depends on the attraction and retention of senior management and scientists with relevant expertise.

Our future success depends to a significant extent on the continued services of our key employees, including our senior scientific, technical and managerial personnel. We do not maintain key man life insurance for any of our executives and we do not maintain employment agreements with most senior officers or employees. Competition for qualified employees in the pharmaceutical industry is high, and our ability to execute our strategy also will depend on our ability to continue to attract and retain qualified scientists and management. If we are unable to find, hire and retain qualified individuals, we will have difficulty implementing our business plan in a timely manner, or at all.

We may have difficulty expanding our operations successfully as we evolve from a company primarily involved in discovery and pre-clinical testing into one that develops and commercializes drugs.

We expect that as we increase the number of product candidates we are developing we will also need to expand our operations. This expected growth may place a strain on our administrative and operational infrastructure. As product candidates we develop enter and advance through clinical trials, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with other organizations to provide these capabilities for us. As our operations expand due to our development progress, we expect that we will need to manage additional relationships with various collaborators, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

Our business and operations could suffer in the event of information technology system failures.

Our internal computer systems and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war, and telecommunication and electrical failures. Such events could cause interruption of our operations and loss of intellectual property. For example, the loss of pre-clinical trial data or data from completed or ongoing clinical trials for our product candidates could result in delays in our regulatory filings and development efforts and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of or damage to our data, or inappropriate disclosure of confidential, proprietary or private information, we could incur liability, we could lose valuable trade secret rights, and the development of our product candidates could be delayed.

Risks related to development and regulatory approval of our product candidates

The manufacture and sale of human therapeutic products are governed by a variety of statutes and regulations. There can be no assurance that our product candidates will obtain regulatory approval.

The sale of human therapeutic products in the U.S. and foreign jurisdictions is subject to extensive and time consuming regulatory approval which requires:

- controlled research and human clinical testing;
- establishment of the safety and efficacy of the product;
- government review and approval of a submission containing manufacturing, pre-clinical and clinical data; and
- adherence to cGMP regulations during production and storage.

The product candidates we currently have under development will require significant development, pre-clinical and clinical testing and investment of significant funds before their commercialization. Some of our product candidates, if approved, will require the completion of post-market studies. There can be no assurance that any of our products will be further developed and approved. The process of completing clinical testing and obtaining required approvals will take a number of years and require the use of substantial resources. Further, there can be no assurance that product candidates employing a new technology will be shown to be safe and effective in clinical trials or receive applicable regulatory approvals. If we fail to obtain regulatory approvals for any or all of our products, we will not be able to market such product and our operations may be adversely affected.

If testing of a particular product candidate does not yield successful results, then we will be unable to commercialize that product candidate.

We must demonstrate our product candidates' safety and efficacy in humans through extensive clinical testing. Our research and development programs are at an early stage of development. We may experience numerous unforeseen events during, or as a result of, the testing process that could delay or prevent commercialization of any products, including the following:

- the results of pre-clinical studies may be inconclusive, or they may not be indicative of results that will be obtained in human clinical trials;
- safety and efficacy results attained in early human clinical trials may not be indicative of results that are obtained in later clinical trials;
- after reviewing test results, we may abandon projects that we might previously have believed to be promising;
- we or our regulators, may suspend or terminate clinical trials because the participating subjects or patients are being exposed to unacceptable health risks; and
- our product candidates may not have the desired effects or may include undesirable side effects or other characteristics that preclude regulatory approval or limit their commercial use if approved.

Clinical testing is very expensive, takes many years, and the outcomes are uncertain. The data collected from our clinical trials may not be sufficient to support approval of our product candidates by the regulatory authorities. The clinical trials of our product candidates may not be completed on schedule, and the regulatory authorities may not ultimately approve any of our product candidates for commercial sale. If we fail to adequately demonstrate the safety and efficacy of a product candidate, it would prevent regulatory approval of the product candidate, which could prevent us from achieving profitability.

It may take us longer than we are currently projecting to complete our clinical trials, and we may not be able to complete them at all.

Although for planning purposes, we project the commencement, continuation and completion of our clinical trials, a number of factors, including scheduling conflicts with participating clinicians and clinical institutions, and difficulties in identifying or enrolling patients who meet trial eligibility criteria, may cause significant delays. We may not commence or complete clinical trials involving any of our product candidates as projected or may not conduct them successfully.

Even if our clinical studies are successful and we achieve regulatory approval, the approved product label may be more limited than we or analysts anticipate, which could limit the commercial opportunity for our product candidates.

At the time drugs are approved for commercialization, they are given a “product label” from the FDA or other regulatory body. In most countries this label sets forth the approved indication for marketing, and identifies potential safety concerns for prescribing physicians and patients. While we intend to seek as broad a product label as possible for our product candidates, we may receive a narrower label than is expected by either us or third parties, such as stockholders and securities analysts. For example, any approved products may only be indicated to treat refractory patients (i.e., those who have failed some other first-line therapy). Similarly, it is possible that only a specific sub-set of patients safely responds to our drug candidates. As a result, our product candidates, even if successful in clinical trials, could be approved only for a subset of patients. Additionally, safety considerations may result in contraindications that could further limit the scope of an approved product label. Any of these or other safety and efficacy considerations could limit the commercial opportunity for our product candidates.

Even if our product candidates are approved for commercialization, future regulatory reviews or inspections may result in the suspension or withdrawal of one or more of our products, closure of a facility or enforcement of substantial fines.

If regulatory approval to sell any of our product candidates is received, regulatory agencies will subject any marketed product(s), as well as the manufacturing facilities, to continual review and periodic inspection. If previously unknown problems with a product or manufacturing and laboratory facility are discovered, or we fail to comply with applicable regulatory approval requirements, a regulatory agency may impose restrictions on that product or on us. The agency may require the withdrawal of the product from the market, closure of the facility or enforcement of substantial fines.

We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability for a product candidate and may have to limit its commercialization.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. Product liability claims might be brought against us by clinical trial participants, consumers, health-care providers, pharmaceutical companies, or others selling our products. If we cannot successfully defend ourselves against these claims, we may incur substantial liabilities. Regardless of merit or eventual outcomes of such claims, product liability claims may result in:

- decreased demand for our product candidates;

- impairment of our business reputation;

- withdrawal of clinical trial participants;

- costs of litigation;

- substantial monetary awards to patients or other claimants;

- loss of revenues; and

- the inability to commercialize our product candidates.

Although we currently have liability insurance for our clinical trials, our insurance coverage may not be sufficient to reimburse us for all expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses.

If a natural or man-made disaster strikes our research and development facility or otherwise affects our business, it could delay our progress developing our product candidates.

We conduct research and development in a facility in Madison, Wisconsin. The facilities and the equipment we use are costly to replace and require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities are affected by a disaster, our development efforts would be delayed. Significant delays in our development efforts could materially impact our ability to obtain regulatory approval and to commercialize our products. Any insurance we maintain against damage to our property and the disruption of our business due to disaster may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

The successful commercialization of our product candidates, if approved, will depend in part on the extent to which government authorities and health insurers establish adequate reimbursement levels and pricing policies.

Sales of any approved drug candidate will depend in part on the availability of coverage and reimbursement from third-party payers such as government insurance programs, including Medicare and Medicaid, private health insurers, health maintenance organizations and other health care related organizations, who are increasingly challenging the price of medical products and services. Accordingly, coverage and reimbursement may be uncertain. Adoption of any drug by the medical community may be limited if third-party payers will not offer coverage. Additionally, significant uncertainty exists as to the reimbursement status of newly approved drugs. Cost control initiatives may decrease coverage and payment levels for any drug and, in turn, the price that we will be able to charge and/or the volume of our sales. We are unable to predict all changes to the coverage or reimbursement methodologies that will be applied by private or government payers. Any denial of private or government payer coverage or inadequate reimbursement could harm our business and reduce our revenue. If we partner with third parties with respect to any of our product candidates, we may be reliant on that partner to obtain reimbursement from government and private payors for the drug, if approved, and any failure of that partner to establish adequate reimbursement could have a negative impact on our revenues and profitability.

In addition, both the federal and state governments in the United States and foreign governments continue to propose and pass new legislation, regulations, and policies affecting coverage and reimbursement rates, which are designed to contain or reduce the cost of health care. Further federal and state proposals and healthcare reforms are likely, which could limit the prices that can be charged for the product candidates that we develop and may further limit our commercial opportunity. There may be future changes that result in reductions in potential coverage and reimbursement levels for our product candidates, if approved and commercialized, and we cannot predict the scope of any future changes or the impact that those changes would have on our operations.

If future reimbursement for approved product candidates, if any, is substantially less than we project, or rebate obligations associated with them are substantially greater than we expect, our net revenue and profitability could be materially and adversely impacted.

We may not enjoy the market exclusivity benefits of our orphan drug designation.

Although we have obtained an orphan designation for ARC-AAT in the treatment of alpha-1 antitrypsin deficiency, ARC-AAT may not be the first product to receive approval for that indication. Under the Orphan Drug Act, the first product with an orphan designation receives market exclusivity, which prohibits FDA from approving the “same” drug for the same indication. The FDA has stated that drugs can be the “same” even when they are not identical, but has not provided guidance with respect to how it will determine “sameness” for RNAi drugs. It is possible that another RNAi drug could be approved for the treatment of alpha-1 antitrypsin deficiency before ARC-AAT, which means that we may not obtain orphan drug exclusivity and could also potentially be blocked from approval until the first product’s orphan drug exclusivity period expires or we demonstrate, if we can, that ARC-AAT is superior. Further, even if we



obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved and granted orphan drug exclusivity, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care.

#### Risks Related to Our Intellectual Property Rights

Our ability to protect our patents and other proprietary rights is uncertain, exposing us to the possible loss of competitive advantage.

We have licensed rights to pending patents and have filed and expect to continue to file patent applications. Researchers sponsored by us may also file patent applications that we may need to license. Such patent applications may not be available for licensing or may not be economically feasible to license. Certain of our patents may not be granted or may not contain claims of the necessary breadth because, for example, prior patents exist. If a particular patent is not granted, the value of the invention described in the patent would be diminished. Further, even if these patents are granted, they may be difficult to enforce. Even if ultimately

successful, efforts to enforce our patent rights could be expensive, distracting for management, cause our patents to be invalidated or held unenforceable, and thus frustrate commercialization of products. Even if patents are issued and are enforceable, others may develop similar, superior or parallel technologies to any technology developed by us and not infringe on our patents. Our technology may prove to infringe upon patents or rights owned by others. Patent prosecution and maintenance is expensive, and we may be forced to curtail prosecution or maintenance if our cash resources are limited. Thus, the patents held by or licensed to us may not afford us any meaningful competitive advantage. If we are unable to derive value from our licensed or owned intellectual property, the value of your investment may decline.

We are party to technology license agreements with third parties that require us to satisfy obligations to keep them effective and, if these agreements are terminated, our technology and our business would be seriously and adversely affected.

We are party to license agreements with Novartis, Alnylam, City of Hope, and other entities to incorporate their proprietary technologies into our drug products under development. These license agreements require us to pay royalties and satisfy other conditions, including conditions in some cases related to the commercialization of the licensed technology. We may not be able to successfully incorporate these technologies into marketable products or, if we do, sales may not be sufficient to recover the amounts that we are obligated to pay to the licensors. If we fail to satisfy our obligations under these agreements, the terms of the licenses may be materially modified, such as by rendering currently exclusive licenses non-exclusive, or it may give our licensors the right to terminate their respective agreement with us, which would limit our ability to implement our current business plan and harm our business and financial condition.

We may be subject to patent infringement claims, which could result in substantial costs and liability and prevent us from commercializing our potential products.

Because the intellectual property landscape in the fields in which we participate is rapidly evolving and interdisciplinary, it is difficult to conclusively assess our freedom to operate without infringing on third party rights. However, we are currently aware of certain patent rights held by third parties that, if found to be valid and enforceable, could be alleged to render one or more of our business lines infringing. If a claim should be brought and is successful, we may be required to pay substantial damages, be forced to abandon any affected business lines and/or seek a license from the patent holder. In addition, any patent infringement claims brought against us, whether or not successful, may cause us to incur significant expenses and divert the attention of our management and key personnel from other business concerns. These could negatively affect our results of operations and prospects. We cannot be certain that patents owned or licensed by us will not be challenged, potentially successfully, by others.

In addition, if our product candidates infringe the intellectual property rights of third parties, these third parties may assert infringement claims against our customers, licensees, and other parties with whom we have business relationships and we may be required to indemnify those parties for any damages they suffer as a result of these claims. The claims may require us to initiate or defend protracted and costly litigation on behalf of customers, licensees, and other parties regardless of the merits of these claims. If any of these claims succeed, we may be forced to pay damages on behalf of those parties or may be required to obtain licenses for the products they use. If we cannot obtain all necessary licenses on commercially reasonable terms, we may be unable to continue selling such products.

We license patent rights from third-party owners and we rely on such owners to obtain, maintain and enforce the patents underlying such licenses.

We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from, among others, Novartis and Alnylam. We also expect to enter into additional licenses to third-party intellectual property in the future.

Our success will depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. Our licensors may not successfully prosecute the patent applications to which we are licensed. Even if patents are issued in respect of these patent applications, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue such litigation less aggressively than we would. Without protection for the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects.

Our technology licensed from various third parties may be subject to retained rights.

Our licensors often retain certain rights under their agreements with us, including the right to use the underlying technology for noncommercial academic and research use, to publish general scientific findings from research related to the technology, and to make customary scientific and scholarly disclosures of information relating to the technology. It is difficult to monitor whether our licensors

limit their use of the technology to these uses, and we could incur substantial expenses to enforce our rights to our licensed technology in the event of misuse.

Confidentiality agreements with employees and others may not adequately prevent disclosure of trade secrets and other proprietary information.

In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our collaborators, employees, consultants, outside scientific collaborators and sponsored researchers, and other advisors. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover trade secrets and proprietary information, and in such cases we could not assert any trade secret rights against such party. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

#### Risks Related to our Stock

Stockholder equity interest may be substantially diluted in any additional financing.

Our certificate of incorporation authorizes the issuance of 145,000,000 shares of Common Stock and 5,000,000 shares of Preferred Stock, on such terms and at such prices as our Board of Directors may determine. The following serves as a summary of share issuance activity during the fiscal year ended September 30, 2015:

- Issued 250,143 shares of Common Stock pursuant to the exercise of stock options, warrants and exchange rights and the vesting of restricted stock units;
- Issued 3,321,383 shares of Common Stock in consideration for the assets acquired as part of the Novartis asset acquisition in March 2015; and
- Issued 1,316,215 shares of Common Stock pursuant to the conversion of certain Preferred Stock held by the Company's shareholders.

As of September 30, 2015, we had 59,544,677 shares of Common Stock issued and outstanding. The issuance of additional securities in financing transactions by us or through the exercise of options or warrants will dilute the equity interests of our existing stockholders, perhaps substantially, and could result in dilution in the tangible net book value of a share of our Common Stock, depending upon the price and other terms on which the additional shares are issued.

Our Common Stock price has fluctuated significantly over the last several years and may continue to do so in the future, without regard to our results of operations and prospects.

Because we are early in the stage of our drug development, there are few objective metrics by which our progress may be measured. Consequently, we expect that the market price of our Common Stock will likely continue to fluctuate significantly. We may not generate substantial revenue from the license or sale of our technology for several years, if at all. In the absence of product revenue as a measure of our operating performance, we anticipate that investors and market analysts will assess our performance by considering factors such as:

Announcements of developments related to our business;

Our ability to enter into or extend investigation phase, development phase, commercialization phase and other agreements with new and/or existing partners;

Announcements regarding the status of any or all of our collaborations or products, including clinical trial results;

Market perception and/or investor sentiment regarding our technology;

Announcements of actions taken by regulatory authorities; such as the U.S. Food and Drug Administration;

Announcements regarding developments in the RNA interference or biotechnology fields in general;

Announcements regarding clinical trial results with our products or competitors' products;

Market perception and/or announcements regarding other companies developing products in the field of biotechnology generally or specifically RNA interference;

The issuance of competitive patents or disallowance or loss of our patent rights;

The addition or departure of key executives; and

Variations in our operating results.

We will not have control over many of these factors but expect that they may influence our stock price. As a result, our stock price may be volatile and such volatility could result in the loss of all or part of your investment.

Litigation claims may result in financial losses or harm our reputation and may divert management resources.

When the market price of a stock is volatile, holders of that stock have often initiated securities class action litigation against the company that issued the stock. Certain of our stockholders have recently brought such lawsuits against us, pursuant to which we could incur substantial costs. We cannot predict with certainty the eventual outcome of this or any other litigation, arbitration or third-party inquiry. We may not be successful in defending ourselves or asserting our rights in current or future lawsuits, investigations, or claims that have been or may be brought against us and, as a result, our business could be materially harmed. These lawsuits, arbitrations, investigations or claims may result in large judgments or settlements against us, any of which could have a negative effect on our financial performance and business. Additionally, lawsuits, arbitrations and investigations can be expensive to defend, whether or not the lawsuit, arbitration or investigation has merit, and the defense of these actions may divert the attention of our management and other resources that would otherwise be engaged in running our business.

The market for purchases and sales of our Common Stock may be limited, and the sale of a limited number of shares could cause the price to fall sharply.

Although our Common Stock is listed for trading on the NASDAQ Global Select Market, at various times our securities have been relatively thinly traded. Investor trading patterns could serve to exacerbate the volatility of the price of our stock. For example, mandatory sales of our Common Stock by institutional holders could be triggered if an investment in our Common Stock no longer satisfies their investment standards and guidelines. It may be difficult to sell shares of our Common Stock quickly without significantly depressing the value of the stock. Unless we are successful in developing continued investor interest in our stock, sales of our stock could result in major fluctuations in the price of the stock.

If securities or industry analysts do not publish research reports about our business or if they make adverse recommendations regarding an investment in our stock, our stock price and trading volume may decline.

The trading market for our Common Stock can be influenced by the research and reports that industry or securities analysts publish about our business. Currently, coverage of our Company by industry and securities analysts is limited. Investors have many investment opportunities and may limit their investments to companies that receive greater coverage from analysts. If additional industry or securities analysts do not commence coverage of the Company, the trading price of our stock could be negatively impacted. If one or more of the analysts downgrade our stock or comment negatively on our prospects, our stock price may decline. If one or more of these analysts cease to cover our industry or us or fail to publish reports about the Company regularly, our Common Stock could lose visibility in the financial markets, which could also cause our stock price or trading volume to decline. Further, incorrect judgments, estimates or assumptions made by research analysts may adversely affect our stock price, particularly if subsequent performance falls below the levels that were projected by the research analyst(s), even if we did not set or endorse such expectations. Any of these events could cause further volatility in our stock price and could result in substantial declines in the value of our stock.

We do not intend to declare cash dividends on our Common Stock.

We will not distribute cash to our stockholders unless and until we can develop sufficient funds from operations to meet our ongoing needs and implement our business plan. The time frame for that is unpredictable and investors

should not expect dividends in the near future, if at all.

Our Board of Directors has the authority to issue shares of “blank check” preferred stock, which may make an acquisition of the Company by another company more difficult.

We have adopted and may in the future adopt certain measures that may have the effect of delaying, deferring or preventing a takeover or other change in control of the Company that a holder of our Common Stock might consider in its best interest. Specifically, our Board of Directors, without further action by our stockholders, currently has the authority to issue up to 5,000,000 shares of preferred stock and to fix the rights (including voting rights), preferences and privileges of these shares (“blank check” preferred). Such preferred stock may have rights, including economic rights, senior to our Common Stock.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

The Company does not own any real property. The following table summarizes the company's leased facilities as of September 30, 2015. The Company does not own any real property.

	Office Space	Monthly Rent	Lease Commencement	Lease Term
Pasadena, California	8,500 sq. ft.	\$24,000	August, 16, 2012	7 years
Madison, Wisconsin	27,000 sq. ft.	\$79,000	February, 16, 2009	10 years
Middleton, Wisconsin	2,900 sq. ft.	\$6,000	May, 18, 2015	1 year

ITEM 3. LEGAL PROCEEDINGS

Legal Proceedings are set forth in our financial statement schedules in Part IV, Item 15 of this Annual Report and are incorporated herein by reference. See Note 7 — Commitments and Contingencies of Notes to Consolidated Financial Statements of Part IV, Item 15. Exhibits and Financial Statement Schedules.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND  
5. ISSUER PURCHASES OF EQUITY SECURITIES

Price Range of Common Stock

Our Common Stock is traded on the NASDAQ Global Select Market under the symbol "ARWR". The following table sets forth the high and low sales prices for a share of the Company's Common Stock during each period indicated.



	Fiscal Year Ended September 30,			
	2015		2014	
	High	Low	High	Low
1st Quarter	\$14.03	\$5.00	\$11.07	\$5.86
2nd Quarter	9.06	6.15	26.57	9.92
3rd Quarter	8.00	6.08	18.28	9.79
4th Quarter	7.62	5.01	16.96	10.72

#### Shares Outstanding

At December 11, 2015, 59,554,677 shares of the Company's Common Stock were issued and outstanding, and were owned by 135 stockholders of record, based on information provided by the Company's transfer agent.

#### Dividends

The Company has never paid dividends on its Common Stock and does not anticipate that it will do so in the foreseeable future.

#### Securities Authorized for Issuance Under the Equity Compensation Plans

The disclosure required under this item related to equity compensation plans is incorporated by reference from Item 12 of Part III of this Annual Report on Form 10-K.

### Sales of Unregistered Securities

All information under this Item has been previously reported on our Current Reports on Form 8-K.

### Repurchases of Equity Securities

We did not repurchase any shares of our Common Stock during the years ended September 30, 2015, 2014 and 2013.

### Performance Graph

The following performance graph shall not be deemed “soliciting material” or to be “filed” with the SEC, nor shall such information be incorporated by reference into any future filing under the Securities Act of 1933 or Securities Exchange Act of 1934, each as amended, except to the extent that we specifically incorporate it by reference into such filing. The graph compares the cumulative 5-year total return to shareholders on our Common Stock relative to the cumulative total returns of the NASDAQ Composite Index and the NASDAQ Biotechnology Index. We selected the NASDAQ Biotechnology Index because we believe the index reflects the market conditions within the industry in which we primarily operate. The comparison of total return on investment, defined as the change in year-end stock price plus reinvested dividends, for each of the periods assumes that \$100 was invested on September 30, 2010, in each of our Common Stock, the NASDAQ Composite Index and the NASDAQ Biotechnology Index, with investment weighted on the basis of market capitalization.

The comparisons in the following graph are based on historical data and are not intended to forecast the possible future performance of our Common Stock.

## ITEM 6. SELECTED FINANCIAL DATA

The following selected financial data has been derived from our audited consolidated financial statements and should be read

in conjunction with the consolidated financial statements, the related notes thereto and the independent auditors' report thereon, and

“Management’s Discussion and Analysis of Financial Condition and Results of Operations,” which are included elsewhere in this

Form 10-K and in previously filed annual reports on Form 10-K of Arrowhead Research Corporation.

	Year Ended September				
	2015	2014	2013	2012	2011
<b>OPERATING SUMMARY</b>					
REVENUE	\$ 382,000	\$ 175,000	\$ 290,266	\$ 146,875	\$ 296,139
<b>OPERATING EXPENSES</b>					
Research and development	47,267,361	23,138,050	8,705,627	5,391,463	3,277,760
Acquired in-process research and development	10,142,786	-	-	-	-
Salaries and payroll-related costs	16,554,008	12,829,355	6,667,669	6,414,921	1,408,366
General and administrative expenses	7,931,184	5,894,008	3,488,864	6,439,323	3,821,550
Stock-based compensation	10,232,897	5,696,173	1,536,271	1,241,404	1,376,921
Depreciation and amortization	2,336,207	1,345,655	1,751,412	1,748,975	241,808
Impairment expense	-	2,172,387	1,308,047	-	-
Contingent consideration - fair value adjustments					