September 13, 2013

Securities and Exchange Commission Division of Corporate Finance 100 F Street, N.E. Washington, D.C. 20549 USA

Attention: Jeffrey P. Riedler - Assistant Director

## Re: Tekmira Pharmaceuticals Corporation (File No. 1-34949) Annual Report on Form 20-F Filed March 27, 2013

Dear Sirs:

On behalf of our client, Tekmira Pharmaceuticals Corporation (the "Company"), we are transmitting for your review the Company's responses to the comments of the staff (the "Staff") of the U.S. Securities and Exchange Commission (the "SEC") set forth your letter, dated August 8, 2013 (the "Comment Letter"), regarding the above-referenced Annual Report on Form 20-F for the year ended December 31, 2012 (the "Form 20-F").

To facilitate the Staff's review, we have included in this letter the comment from the Comment Letter in bold text, as well as an additional comment delivered by telephone, and have provided the Company's responses immediately following the numbered comments below.

# TKM Ebola, page 21

# Partnerships and Collaborations, pages 22-25

1. We note that you provide a discussion of material contracts under the above-mentioned captions. Please expand your disclosure to discuss the duration and termination provisions of the following agreements:

· Contract with the United States Department of Defense (DoD), under their TMT program, to advance an RNAi therapeutic utilizing our LNP technology to treat Ebola virus infection;

· Settlement agreement between Tekmira and Alnylam and AlCana Technologies, Inc.;

- · New licensing agreement with Alnylam;
- · Licensing and collaboration agreement with Halo-Bio;

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U.S. Securities and Exchange Commission September 13, 2013 Page 2

- · Licensing agreement with Marina Biotech;
- · Non-exclusive royalty-bearing world-wide license agreement between Merck and Protiva;
- · Research collaboration agreement with Bristol-Myers Squibb;
- · Licensing agreement with Talon Therapeutics Inc.;
- $\cdot$  Licensing agreement with Aradigm; and
- · Licensing agreement with the University of British Columbia.

The Company intends to make the requested revisions in Item 4.B of an amendment to the Form 20-F (the "Amendment"). A draft of the revised Item 4.B., which is marked to show the applicable revisions thereto, is attached hereto as Appendix I.

# 2. Additional Telephonic Comment

In response to a comment received telephonically from the Staff the Company (i) hereby amends the Confidential Treatment Application filed by the Company and received by the SEC on March 28, 2013 to reinstate the redaction appearing under the table in Section 4.3(b) of Exhibit 4.28 filed with the Form 20-F and (ii) will re-file such version of Exhibit 4.28 as part of the Amendment.

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As always, should you have further comments or require further information, or if any questions should arise in connection with this submission, please call the undersigned at (604) 630-5199. You also may contact the undersigned be email at miller.dan@dorsey.com or by fax at (604) 687-8504.

Yours truly,

/s/ Daniel M. Miller Daniel M. Miller

cc: Ian Mortimer, Tekmira Pharmaceuticals Corporation



## 4B. Business Overview

### **Business Strategy**

Tekmira's business strategy is to develop our proprietary RNAi therapeutic product candidates and to support our pharmaceutical partners as they advance their own RNAi product candidates using our lipid nanoparticle (LNP) delivery technology.

#### Technology, product development and licensing agreements

Our therapeutic product pipeline consists of products being developed internally with our research and development resources. We also support the development of our partners' products and are developing an Ebola antiviral product, called TKM-Ebola, under a Transformational Medical Technologies (TMT) contract with the U.S. Government. Our focus is on advancing products that utilize our proprietary LNP technology for the delivery of small interfering RNA (siRNA), multivalent RNA (MV-RNA), or Unlocked Nucleobase Analogs (UNA). These products are intended to treat diseases through a process known as RNA interference, which prevents the production of disease associated proteins. We have rights under the RNAi intellectual property of Alnylam Pharmaceuticals, Inc. to develop thirteen RNAi therapeutic products. In addition, we have exclusive access to use MV-RNA technology from Halo-Bio RNAi Therapeutics, Inc. and non-exclusive access to use UNAs from Marina Biotech, Inc. for the development of RNAi therapeutic products.

In the field of RNAi therapeutics, we have licensed our LNP delivery technology to Alnylam and Merck & Co., Inc., and Alnylam has provided certain access to our LNP delivery technology to some of its partners. In addition, we have ongoing research relationships with Bristol-Myers Squibb Company, the United States National Cancer Institute, the U.S. Government, through their TMT program, and other undisclosed pharmaceutical and biotechnology companies. Outside the field of RNAi, we have legacy licensing agreements with Talon Therapeutics, Inc. and Aradigm Corporation.

### **RNA Interference Therapeutics**

RNAi is considered to be one of the most important discoveries in the field of biology in the last decade. The scientists who discovered the mechanism were awarded the 2006 Nobel Prize in Medicine. Intense research activity has subsequently uncovered the complex molecular mechanisms responsible for RNAi that are transforming the way that drug targets are discovered and validated. RNAi is a naturally occurring process that takes place inside cells, and includes processes whereby siRNA molecules profoundly suppress the production of specific proteins. Synthetic siRNA molecules are being developed as drugs that specifically suppress the production of disease-related proteins through RNAi.

In the cell, DNA carries the genetic information required to make each specific protein. Genes are first copied or transcribed into messenger RNA (mRNA), which, in turn, is translated into protein. Nearly all diseases are caused by either the absence of or over-production of a specific protein. If too much of a particular protein is the cause of disease then the therapeutic approach is to try to reduce its activity or amount. For example, a tumor can be caused by the over-production of a protein that stimulates cell growth.



Sequencing of the human genome has unlocked the information needed to design siRNA molecules directed against a wide range of disease-causing proteins. Using the mRNA sequence coding for the target protein, effective siRNA molecules can be designed much more rapidly than the time needed to synthesize and screen conventional drugs. siRNA-based drugs are short segments of synthetic double stranded RNA made up of a sense strand and an antisense strand. The sequence of the siRNA is designed so that the antisense strand will bind specifically to a complementary sequence on the mRNA coding for the target protein. When siRNA are introduced into the cell they are rapidly incorporated into an RNA-induced silencing complex (RISC). As illustrated in the diagram below, during this process the sense strand is unwound and discarded while the antisense strand remains in the RISC serving to guide the RISC complex to interact specifically with mRNA coding for the target protein. mRNA are cleaved in a sequence specific manner and then destroyed, preventing production of the target protein. Importantly, this process is catalytic and RISC associated siRNA can remain stable inside the cell for weeks, destroying many more copies of the target mRNA and maintaining target protein suppression for long periods of time.



Lipid Nanoparticle (LNP)-Enabled Delivery of siRNA and Mechanism of RNA Interference in Cells

RNAi has the potential to generate a broad new class of therapeutics that take advantage of the body's own natural processes to silence genes—or more specifically to eliminate specific gene-products, from the cell. While there are no RNAi therapeutics currently approved for commercial use, there are a number of RNAi products in development and several in human clinical trials. RNAi products are broadly applicable as they can silence, or eliminate the production of disease causing proteins from cells, thus creating opportunities for therapeutic intervention that have not been achievable with conventional drugs. Development of RNAi

therapeutic products is currently limited by the instability of the siRNA molecules in the bloodstream and the inability of these molecules to access target cells or tissues following intravenous, or systemic, administration, and their inability to gain entry to the inside of target cells, where they carry out their action. Delivery technology is necessary to protect these drugs in the blood stream following administration, allow efficient delivery to the target cells and facilitate cellular uptake and release into the cytoplasm of the cell. Tekmira's LNP technology has been shown in pre-clinical studies to enable RNAi therapeutic products by overcoming these limitations, allowing efficient and selective 'silencing' or reduction of certain target proteins. We believe that Tekmira is strongly positioned to take advantage of the need for delivery technology that can efficiently encapsulate siRNA molecules and deliver them to sites of disease. We and our partners are advancing RNAi therapeutic product candidates using our LNP technology as the delivery vehicle to access target tissues and cells.

### Tekmira's LNP Technology

Our LNP delivery technology allows siRNA to be encapsulated in a particle made of lipids (fats or oils) that can be administered intravenously and travel through the blood stream to target tissues or sites of disease. The nanoparticles are designed to stay in the circulation for periods of time that allow the particle to efficiently accumulate at sites of disease such as the liver or cancerous tumors. As illustrated in the diagram above, once the nanoparticles have accumulated at the target site, the cells take up the particle by a process called endocytosis in which the cell's membrane surrounds the particle. This envelope or endosome pinches off from the cell's membrane and migrates to the inside of the cell. The lipid nanoparticles undergo an interaction with the endosomal membrane and in the process the siRNA are released inside the cell. The released siRNA molecules engage the RISC complex, mediating RNAi.

### **Internal Product Development**

# TKM-PLK1

Our lead oncology product candidate, TKM-PLK1, has been shown in preclinical animal studies to selectively kill cancer cells, while sparing normal cells in adjacent healthy tissue. TKM-PLK1 targets PLK1 (polo-like kinase 1), a protein involved in tumor cell proliferation and a validated oncology target. Inhibition of PLK1 expression prevents the tumor cell from completing cell division, resulting in cell cycle arrest and death of the cancer cell.

Our preclinical studies have demonstrated that a single, systemic intravenous administration of TKM-PLK1 blocked PLK1 expression in liver tumors causing extensive tumor cell death. After repeat dosing, this result translated into significant inhibition of tumor growth and prolonged survival without evidence of the toxicities often associated with oncology drugs. The TKM-PLK1 anti-tumor efficacy results were confirmed to be the result of silencing PLK1 via RNA interference. Furthermore, certain LNP formulations provided anti-tumor efficacy in preclinical models of tumors outside the liver.

On December 22, 2010, we announced the initiation of patient treatment in a Phase 1 human clinical trial of TKM-PLK1. The Phase 1 clinical trial, conducted at medical centers in the United States, is an open label, multi-dose, dose escalation study designed to evaluate the safety, tolerability and pharmacokinetics of TKM-PLK1 as well as determining the maximum tolerated dose. The trial is enrolling patients with advanced solid tumors. Secondary objectives of the trial are to measure tumor response and the pharmacodynamic effects of TKM-PLK1 in patients providing biopsies.

On August 14, 2012, we released interim results from our TKM-PLK1 Phase 1 clinical trial showing that TKM-PLK1 was generally well tolerated and highlighting evidence of drug activity, including one patient with a partial response and another patient who attained stable disease. Based on these interim data, patient enrollment is continuing at 0.75 mg/kg. Once complete, results from the Phase 1 clinical trial, including additional measures of drug activity, will be presented at forthcoming scientific meetings. Tekmira anticipates initiating a TKM-PLK1 Phase 2 clinical trial in 2013.

### TKM-Ebola

For many years, the Zaire species of Ebola virus (ZEBOV) has been associated with periodic outbreaks of hemorrhagic fever in human populations with mortality rates reaching 90%. There are no approved treatments for Ebola or other hemorrhagic fever viruses.

On May 28, 2010 we announced the publication of a series of studies demonstrating the ability of an RNAi therapeutic utilizing our LNP technology to protect non-human primates from Ebola virus, a highly contagious and lethal human infectious disease. We conducted the studies in collaboration with infectious disease researchers from Boston University and the United States Army Medical Research Institute for Infectious Diseases (USAMRIID) and were funded in part by the U.S. Government's Transformational Medical Technologies (TMT) program. These preclinical studies were published in the medical journal The Lancet and demonstrated that when siRNA targeting the Ebola virus and delivered by Tekmira's LNP technology were used to treat previously infected non-human primates, the result was 100 percent protection from an otherwise lethal dose of Zaire Ebola virus (Geisbert et al., The Lancet, Vol 375, May 29, 2010).

On July 14, 2010, we signed a contract with the United States Department of Defense (DoD), under their TMT program, to advance an RNAi therapeutic utilizing our LNP technology to treat Ebola virus infection. In the initial phase of the contract, we are eligible to receive up to US\$34.7 million. This initial funding is for the development of TKM-Ebola, including completion of preclinical development, filing an IND application with the FDA and the completion of a Phase 1 human safety clinical trial. <u>The initial funding stage and completion of the Phase 1 clinical trial is expected to be completed in the second half of 2014.</u>

The United States DoD has the option of extending the contract beyond the initial funding period to support the advancement of TKM-Ebola through to the completion of clinical development and FDA approval. Based on the budget for the extended contract this would provide the Company with a total of up to US\$140.0 million in funding for the entire program. Under the contract we invoice the United States DoD for direct labor, third party costs and an apportionment of overheads plus an incentive fee. The funding is paid through monthly reimbursements, and the United States DoD has the ability to cancel at any time.

On August 6, 2012, we announced that we had received a temporary stop-work order from the United States DoD with respect to our TKM-Ebola program. On October 2, 2012, we disclosed that the temporary stop-work order was lifted by the United States DoD and work is now continuing on the development of the TKM-Ebola product.

In November 2012, we disclosed that we have submitted a modification request to the existing contract to the DoD in order to integrate recent advancements in LNP formulation and manufacturing technology in the TKM-Ebola development program. Tekmira has initiated pre-clinical and chemistry, manufacturing and control studies that support the use of these improvements in the program. This development strategy will be accommodated by

modifications to the existing contract, allowing both Tekmira and TMT to benefit from the significant advancements in LNP formulation technology made by Tekmira since the commencement of the TMT-funded program in July 2010. The contract modification request is currently being negotiated while work is continuing on the contract. It is expected that the LNP formulation work will be completed and submitted to the FDA in the second half of 2013 in order to initiate a new Phase 1 clinical trial.

TKM-Ebola is being developed under specific FDA regulatory guidelines called the "Animal Rule." The Animal Rule provides that under certain circumstances, where it is unethical or not feasible to conduct human efficacy studies, the FDA may grant marketing approval based on adequate and well-controlled animal studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans. Demonstration of the product's safety in humans is still required.

# Additional Product Candidates

We have a number of other preclinical candidates in our pipeline addressing a wide range of therapeutic needs such as alcohol dependence and additional oncology targets. We will continue to generate data to support the advancement of the most promising of these targets, and we expect to be in a position to nominate our next product candidate for development in 2013.

#### Partnerships and Collaborations

#### Alnylam collaborations and licenses

On November 12, 2012, we entered into an agreement to settle all litigation between Tekmira and Alnylam and AlCana Technologies, Inc., and we also entered into a new licensing agreement with Alnylam that replaces all earlier licensing, cross-licensing, collaboration, and manufacturing agreements. Tekmira expects to enter into a separate cross license agreement with AlCana which will include milestone and royalty payments and AlCana has agreed not to compete in the RNAi field for five years. In conjunction with the Settlement, we paid AlCana US\$300,000 and accrued a further US\$1,500,000, which we expect to pay upon the execution of a cross license agreement with AlCana.

As a result of the new Alnylam license agreement, Tekmira received a total of US\$65 million in cash payments in November 2012. This includes US\$30 million associated with the termination of the manufacturing agreement and US\$35 million associated with the termination of the previous license agreements, as well as a reduction of the milestone and royalty schedules associated with Alnylam's ALN-VSP, ALN-PCS, and ALN-TTR programs. Of the US\$65 million received from Alnylam, US\$18.7 million was subsequently paid by us to our lead legal counsel representing us in the lawsuit against Alnylam and AlCana, in satisfaction of the contingent obligation owed to that counsel. We are also eligible to receive an additional US\$10 million in near-term milestones, comprised of a US\$5 million payment upon ALN-TTR entering a Phase 3 or pivotal clinical trial and a US\$5 million payment related to enabling drug production for the initiation of clinical trials for ALN-VSP in China. Both near-term milestones are expected to occur in 2013. In addition, Alnylam has transferred all agreed upon patents and patent applications related to LNP technology for the systemic delivery of RNAi therapeutic products, including the MC3 lipid family, to Tekmira, and we will own and control prosecution of this intellectual property portfolio. Tekmira is the only company able to sublicense LNP intellectual property in future platform-type relationships. Alnylam has a license to use Tekmira's intellectual



property to develop and commercialize products and may only grant access to Tekmira's LNP technology to its partners if it is part of a product sublicense. Alnylam will pay Tekmira milestones and royalties as Alnylam's LNP-enabled products are developed and commercialized.

The new licensing agreement with Alnylam also grants us intellectual property rights to develop our own proprietary RNAi therapeutics. Alnylam has granted us a worldwide license for the discovery, development and commercialization of RNAi products directed to thirteen gene targets – three exclusive and ten non-exclusive licenses – provided that they have not been committed by Alnylam to a third party or are not otherwise unavailable as a result of the exercise of a right of first refusal held by a third party or are part of an ongoing or planned development program of Alnylam. Licenses for five of the ten non-exclusive targets – ApoB, PLK1, Ebola, WEE1, and CSN5 – have already been granted, along with an additional license for ALDH2, which has been granted on an exclusive basis. In consideration for this license, we have agreed to pay single-digit royalties to Alnylam on product sales and have milestone obligations of up to US\$8.5 million on the non-exclusive licenses (with the exception of TKM-Ebola, which has no milestone obligations). Alnylam no longer has "opt-in" rights to Tekmira's lead oncology product, TKM-PLK1, so we now hold all development and commercialization rights related TKM-PLK1. We will have no milestone obligations on the three exclusive licenses.

Alnylam currently has three LNP-enabled products in human clinical trials: ALN-TTR, ALN-VSP, and ALN-PCS.

Alnylam's ALN-TTR01 and ALN-TTR02 are RNAi therapeutics targeting transthyretin (TTR) for the treatment of TTR-mediated amyloidosis (ATTR), a systemic disease caused by mutations in the TTR gene. ALN-TTR01 and ALN-TTR02 utilize our LNP technology. In July 2010, Alnylam announced the initiation of a Phase 1 human clinical trial for ALN-TTR01, which triggered a US\$0.5 million milestone payment to us. Alnylam also initiated a Phase 1 trial with ALN-TTR02 aimed at evaluating safety, tolerability, and clinical activity of ALN-TTR02. New data were presented on July 16, 2012 at Boston University School of Medicine. Alnylam reported results that showed that administration of ALN-TTR02 resulted in statistically significant reductions in serum TTR protein levels of up to 94%. Suppression of TTR, the disease-causing protein in ATTR, was found to be rapid, dose dependent, durable, and specific after just a single dose. Alnylam has initiated a Phase 2 study of ALN-TTR02 in patients with ATTR and has guided that its goal is to start a Phase 3 clinical trial by the end of 2013. The initiation of the Phase 2 study of ALN-TTR02 triggered a US\$1.0 million milestone payment to Tekmira. Tekmira is entitled to receive a US\$5 million milestone payment when ALN-TTR02 enters a Phase 3 or pivotal clinical trial, which is expected to occur in 2013. Tekmira will also receive low single digit royalty payments based on commercial sales of ALN-TTR02.

In April 2009, Alnylam announced that they had initiated a Phase 1 human clinical trial for ALN-VSP. ALN-VSP is being developed as a treatment for advanced solid tumors with liver involvement. ALN-VSP comprises siRNA molecules delivered systemically using our LNP technology. The initiation of the ALN-VSP Phase 1 clinical trial triggered a milestone payment of \$0.6 million (US\$0.5 million) which we received in May 2009. In June 2011, Alnylam presented Phase 1 human clinical trial data at American Society of Clinical Oncology (ASCO) meeting and disclosed that ALN-VSP was generally well tolerated, demonstrated evidence for anti-tumor activity, and was found to mediate RNAi activity in both hepatic and extra-hepatic tumors. The most recent ALN-VSP data were presented at the American Society of Clinical Oncology (ASCO) meeting in June 2012. Alnylam disclosed that, overall, the results demonstrated

disease control lasting more than six months in the majority of patients treated on the extension study, including a complete response (CR) in an endometrial cancer patient who had multiple liver metastases. In this study, chronic dosing of up to 23 months with ALN-VSP was found to be generally safe and well tolerated. In July 2012, Alnylam disclosed that it has formed a strategic alliance with Ascletis Pharmaceuticals (Hangzhou) Co., Ltd., a privately held US-China joint venture pharmaceutical company, to develop and commercialize ALN-VSP in China, including Hong Kong, Macau, and Taiwan. Tekmira is entitled to receive a US\$5 million milestone payment for enabling ALN-VSP to enter clinical trials in China, which is expected to occur in 2013. Tekmira will also receive low single digit royalty payments based on commercial sales of ALN-VSP.

Alnylam is also developing ALN-PCS, an RNAi therapeutic, which is enabled by our LNP delivery technology, to treat hypercholesterolemia, or high levels of cholesterol in the blood. On September 26, 2011, Alnylam announced the initiation of a Phase 1 human clinical trial for ALN-PCS which triggered a US\$0.5 million milestone payment to us. On April 20, 2012, Alnylam presented ALN-PCS data at the American Heart Association's Arteriosclerosis, Thrombosis, and Vascular Biology (ATVB) 2012 Scientific Sessions held in Chicago, IL. Alnylam reported results that showed that administration of a single dose of ALN-PCS, in the absence of concomitant lipid-lowering agents such as statins, resulted in statistically significant and durable reductions of PCSK9 plasma levels of up to 84% and lowering of low-density lipoprotein cholesterol (LDL-C), or "bad cholesterol," of up to 50%. ALN-PCS was shown to be safe and well tolerated in this study. In February 2013, Alnylam disclosed an exclusive global alliance with The Medicines Company to advance the ALN-PCS program. Tekmira will receive low single digit royalty payments based on commercial sales of ALN-PCS.

The Alnylam license agreement generally ends upon the expiration of the last to expire royalty term, which duration is determined on a product-byproduct and country-by-country basis, commencing on the first commercial sale and continuing during any period in which a product sold is covered by a valid claim of a licensed patent granted by one party of the agreement to the other party. Either party may terminate a license it granted to the other in the event that the other party fails to cure a material breach of its obligation under the agreement. In addition, either party may terminate the agreement upon patentrelated challenges by the other party.

## License and collaboration agreement with Halo-Bio RNAi Therapeutics, Inc. (Halo-Bio)

On August 24, 2011, we entered into a license and collaboration agreement with Halo-Bio. Under the agreement, Halo-Bio granted to us an exclusive license to its multivalent ribonucleic acid MV-RNA technology. The Agreement allows us to work together with Halo-Bio to design and develop MV-RNA molecules directed at gene targets of interest to us and to combine MV-RNA molecules with our LNP technology to develop therapeutic products. MV-RNA technology comprises single macromolecules capable of mediating RNAi at multiple unique target sites. MV-RNA can target three sites on a single gene or up to three separate genes simultaneously. We have already successfully demonstrated multi-gene knockdown using MV-RNA enabled by our proprietary LNP formulations.

The agreement was amended on August 8, 2012 to adjust the future license fees and other contingent payments. We have recorded \$0.5 million in fees under our license from Halo-Bio to

the end of 2012. Under the amended agreement, the maximum future license fees and other contingent payments are US\$1.3 million and we will pay up to US\$12.7 million in milestones on each product developed plus royalties. <u>This license was terminated by Tekmira for convenience effective as of July 31, 2013</u>

# License agreement with Marina Biotech, Inc.

On November 29, 2012, we disclosed that we had obtained a worldwide, non-exclusive license to a novel RNAi payload technology called Unlocked Nucleobase Analog (UNA) from Marina for the development of RNAi therapeutics. UNA technology can be used in the development of RNAi therapeutics, which treat disease by silencing specific disease causing genes. UNAs can be incorporated into RNAi drugs and have the potential to improve them by increasing their stability and reducing off-target effects. Marina will receive an upfront payment plus milestone and royalty payments on products developed by Tekmira that use UNA technology. In December 2012, we paid Marina an up-front license fee of \$0.3 million. We expect to pay Marina a further license fee of US\$0.2 million in Q2 2013 and there are milestones of up to US\$3.2 million plus royalties for each product that we develop using UNA technology licensed from Marina.

Unless terminated earlier, the license grants by Marina expire on a country-by-country basis, upon the earlier of: (i) the expiry of the Royalty Term for each licensed product in such country, or (ii) the end of the calendar quarter in which sales in such country of generics exceed 50% of the sales of licensed product in such country. Royalty Term is defined in the license agreement as a period extending to the later of: (a) the date of the last to expire issued licensed patent having a valid claim covering the licensed product; or (b) 10 years after the date of first commercial sale of a licensed product in a major market (US, UK, France, Germany, Italy, Spain, China or Japan). We may terminate the license agreement for convenience, and either party may terminate the license agreement for bankruptcy or for a material breach which remains uncured. We may cure a default in payment within 60 days following receipt of Marina's notice, or cure any other default within 120 days following receipt of Marina's notice. Marina may cure any default within 120 days following receipt of our notice. If Marina fails to cure a material breach, at our sole option, (i) the licenses granted by Marina will automatically convert into a worldwide, royalty-free, fully paid-up, perpetual license; or (ii) we may terminate the license agreement in its entirety or in respect of any country or countries.

### Roche product development and research agreements

On May 30, 2008, we signed an initial research agreement with Roche. This initial research agreement expired at the end of 2008 and was replaced by a research agreement (Roche Research Agreement) dated February 11, 2009. Work under the Roche Research Agreement was completed in the first half of 2009.

On May 11, 2009 we announced a product development agreement with Roche (Roche Product Development Agreement) that provides for product development up to the filing of an IND by Roche. The product development activities under this agreement expand the activities that were formerly covered by the Roche Research Agreement. Under the Roche Product Development Agreement Roche paid for the provision of our staff and for external costs incurred up to US\$8.8 million, for us to support the advancement of a Roche RNAi product candidate using our LNP technology through to the filing of an IND application.



On November 17, 2010, Roche announced that, as part of a corporate restructuring, they intend to discontinue research and development in the field of RNAi. Following the announcement, Roche confirmed that, except for completing some product stability studies, they would be discontinuing product development with Tekmira. The stability studies were completed in 2011 so we now have no further obligation to Roche. In October 2011, Arrowhead Research Corporation announced that it had acquired all RNA therapeutics assets and intellectual property from Roche.

#### Merck license agreement

Protiva, our wholly owned subsidiary, is party to a non-exclusive royalty-bearing world-wide license agreement with Merck. Under the license, Merck will pay up to US\$17.0 million in milestones for each product they develop covered by Protiva's intellectual property, except for the first product, for which Merck will pay up to US\$15.0 million in milestones, and will pay single-digit royalties on product sales. Merck has also granted a <u>non-exclusive, perpetual</u>, <u>royalty-free</u> license to us, <u>with the right to grant sublicenses</u>, for some of its patents. The license agreement with Merck was entered into as part of the settlement of litigation between Protiva and a Merck subsidiary. <u>The royalty payable by Merck to us will expire upon the expiry of the last valid claim in an issued and unexpired patent within the Protiva Patent Rights or Collaboration Patent Rights. No termination provisions exist in the licenses granted under the <u>Merck agreement</u>.</u>

### Bristol-Myers Squibb research agreement

On May 10, 2010 we announced the expansion of our research collaboration with Bristol-Myers Squibb. Under the new agreement, Bristol-Myers Squibb will use siRNA molecules formulated by us in lipid nanoparticles to silence target genes of interest. Bristol-Myers Squibb will conduct the pre-clinical work to validate the function of certain genes and share the data with us. We can use the pre-clinical data to develop RNAi therapeutic products against the therapeutic targets of interest. Bristol-Myers Squibb paid us US\$3.0 million concurrent with the signing of the agreement. We are required to provide a pre-determined number of lipid nanoparticle batches over the four-year agreement. Bristol-Myers Squibb will have a first right to negotiate a licensing agreement on certain RNAi products developed by us that evolve from Bristol-Myers Squibb validated gene targets. On May 17, 2011 we announced a further expansion of the collaboration to include broader applications of our LNP technology and additional target validation work.

Unless earlier terminated, the research collaboration with Bristol-Myers Squibb will continue through May 6, 2014. Bristol-Myers Squibb may terminate the agreement at any time with 60 days' prior written notice. Either party may terminate the agreement if the other party undergoes a change of control so long as the terminating party gives the other party or the other party's successor at least 30 days' prior written notice of termination, which notice is given before the 90th day following the change of control. Each party may also terminate the agreement if the other party fails to cure a material breach within 90 days after receipt of a notice of breach from the non-breaching party; provided however, that if the breach is disputed in good faith, the 90-day cure period will not begin until the earlier of (i) the date such dispute is resolved or can no longer be maintained in good faith, or (ii) the 120th day following the receipt of notice of breach, unless either party has, prior to such 120th day, commenced an arbitration proceeding to resolve such dispute as to the existence of the breach.



### USAMRIID research agreement

In 2005 we signed a five-year research agreement with the United States Army Medical Research Institute for Infectious Diseases (USAMRIID) to collaborate on the development of siRNA-based therapy against filovirus infections, including Ebola, using LNPs. In 2010 we received the final payment under this grant. Further development of our TKM-Ebola product is being funded by the U.S. Department of Defense under the Transformational Medical Technologies (TMT) program as discussed in *"TKM-Ebola"* section above.

# U.S. National Institutes of Health (NIH) grant

On October 13, 2010 we announced that together with collaborators at The University of Texas Medical Branch (UTMB), we were awarded a new NIH grant to support research to develop RNAi therapeutics to treat Ebola and Marburg hemorrhagic fever viral infections using our LNP delivery technology. The grant, worth US\$2.4 million, is supporting work at Tekmira and the UTMB.

### Legacy Agreements

# Talon Therapeutics, Inc. (Talon, formerly Hana Biosciences, Inc.) license agreement

Talon is developing targeted chemotherapy products under a legacy license agreement entered into in May 2006. Marqibo (Optisomal Vincristine), Alocrest (Optisomal Vinorelbine) and Brakiva (Optisomal Topotecan), products originally developed by us, have been exclusively licensed to Talon. Talon has agreed to pay us milestones and single-digit royalties and is responsible for all future development and future expenses. In May 2009, the license agreement with Talon was amended to decrease the size of near-term milestone payments and increase the size of long-term milestone payments. On September 20, 2010, the license agreement with Talon was amended a second time such that Talon paid \$5.9 million (US\$5.75 million) in consideration for reducing certain future payments associated with the product candidates. The payment of \$5.9 million (US\$5.75 million) from Talon has been paid to our contingent creditors in full settlement of a contingent obligation. We are now eligible to receive milestone payments from Talon of up to US\$18.0 million upon achievement of further development and regulatory milestones and, we will also receive single-digit royalties based on product sales. If Talon sublicenses any of the product candidates, Tekmira is eligible to receive a percentage of any upfront fees or milestone payments received by Talon. Depending on the royalty rates Talon receives from its sublicensees, our royalty rate may be lower on product sales by the sublicensees. The royalty rate will be reduced to low single digits if there is generic competition.

Marqibo is a proprietary sphingosomal formulation of the widely used, off-patent cancer chemotherapeutic vincristine. The FDA has granted Talon orphan drug and fast track designations for the use of Marqibo in adult acute lymphoblastic leukemia (ALL). In August 2007, Talon initiated a Phase 2 Marqibo registration-enabling clinical trial in relapsed ALL. On July 18, 2011, Talon announced that its New Drug Application (NDA) for Marqibo had been submitted to the FDA seeking approval for the treatment of adult Philadelphia chromosome-negative ALL in second or greater relapse or that has progressed following two or more lines of anti-leukemia therapy. On August 9, 2012, Talon announced that Marqibo<sup>®</sup> (vinCRIStine sulfate LIPOSOME injection) had received accelerated approval from the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has

progressed following two or more anti-leukemia therapies. Talon is responsible for all future development of Marqibo. In 2012, we received a US\$1.0 million milestone payment based on the FDA approval of Marqibo and will receive mid-single digit royalty payments based on Marqibo's commercial sales.

Unless terminated earlier, the license grants made under the license agreement expire on a country-by-country basis upon the later of (i) the expiration of the last to expire patents covering each product in a particular country, (ii) the expiration of the last to expire period of product exclusivity covered by a product under the laws of such country, or (iii) on the date that all of the licensed Technology ceases to be confidential information of Tekmira.

Either party may terminate the license agreement in the event that the other has materially breached its obligations thereunder and fails to remedy such breach within 90 days following notice by the non-breaching party. If such breach is not cured, then the non-breaching party may, upon 6 months' notice to the breaching party, terminate the license in respect of the products or countries to which the breach relates. Tekmira may also terminate the license if Talon asserts or intends to assert any invalidity challenge on any of the licensed patents. The license agreement also provides that either party may, upon written notice, terminate the agreement in the event of the other's bankruptcy, insolvency, dissolution or similar proceeding. In the event Tekmira validly terminates the license agreement, all data, materials, regulatory filings and all other documentation reverts to Tekmira.

### Aradigm Corporation license agreement

In December 2004, we entered into a licensing agreement with Aradigm under which Aradigm exclusively licensed certain of our liposomal intellectual property for the pulmonary delivery of Ciprofloxacin. As amended, this agreement calls for milestone payments totalling US\$4.5 and US\$4.75 million, respectively, for the first two disease indications pursued by Aradigm using our technology, and for low- to mid-single-digit royalties on sales revenue from products using our technology. Aradigm has asserted that it is not using our technology in its current products. The parties mutually agreed to terminate the license effective May 9, 2013; provided however, that Tekmira retains the right to seek damages if Aradigm breaches one or more representations and warranties contained in the Letter of Termination, relating to Aradigm, its affiliates or sublicensees (i) receiving any milestones or net sales so as to trigger payment obligations under the license agreement; (ii) creating any intellectual property rights arising from the development of licensed product that would entitle Tekmira to such intellectual property rights; or (iii) using any licensed patents or licensed know-how for the research, development, manufacture or commercialization of any product or technology.

### University of British Columbia

Certain early work on lipid nanoparticle delivery systems and related inventions was undertaken at the University of British Columbia (UBC). These inventions are licensed to us by UBC under a license agreement, initially entered in 1998 and thereafter restated and amended. This agreement calls for revenue sharing on payments received from sublicenses that range from 10% for intellectual property related to certain technology used for the delivery of oligonucleotides and up to approximately 20% for intellectual property covering certain legacy product candidates being advanced by Talon and Aradigm. The agreement calls for single-digit royalties on product sales made by us under the licensed patents. The patents licensed to us by UBC under this license agreement have been expanded over the years to include patents, if

any, on additional inventions discovered by UBC and us in our prior collaborations with UBC or otherwise in the course of our prior collaboration with Alnylam. These collaborations with UBC and with Alnylam ended at the end of 2008. We have granted sublicenses under the UBC license to Alnylam as well as to Talon and Aradigm. While Alnylam's sublicense is exclusive in the RNAi field, Alnylam has in turn sublicensed us under the licensed UBC patents for discovery, development and commercialization of RNAi products. <u>Unless earlier terminated, the agreement between UBC and Tekmira will expire upon the later of (i) July 1, 2018 or (ii) the expiration, on a country-by-country basis, of the last claim of any licensed issued patent or licensed pending patent that has been pending less than 6 years from its filing date.</u>

Tekmira may terminate this license for convenience. This license terminates automatically without notice if Tekmira undergoes bankruptcy or insolvency, except for involuntary bankruptcy or insolvency proceedings, in which case Tekmira will have 60 days to have the proceedings against it discharged to avoid termination. UBC may terminate this license with notice, with immediate effect, if Tekmira grants any sublicense without the prior written consent of UBC, notifies UBC that Tekmira will cease pursuing all patent protection for the licensed technology, or fails to cure within 60 days of UBC's notice to Tekmira, a material breach of a sublicense by Tekmira's sublicensee, which if committed by Tekmira would constitute a breach of the UBC license. Other than the foregoing termination rights, either party may terminate this license upon the other party's failure to cure any breach within 90 days after receipt of written notice of breach.

In mid-2009, we and our subsidiary Protiva entered into a supplemental agreement with UBC, Alnylam and AlCana Technologies, Inc., in relation to a separate research collaboration to be conducted among UBC, Alnylam and AlCana. We are licensed under the supplemental agreement to inventions discovered from this collaboration. <u>Notwithstanding the termination of the supplemental agreement on November 12, 2012, Tekmira and Protiva continue to receive a milestone and royalty-bearing license from UBC to inventions discovered prior to termination of this agreement. Payment obligations cease upon the expiration, on a country-by-country basis, of the last claim of any licensed issued patent or licensed pending patent that has been pending less than 5 years from its filing date.</u>

## Patents and Proprietary Rights

In addition to the expertise we have developed and maintain in confidence, we own a portfolio of patents and patent applications directed to LNP inventions, the formulation and manufacture of LNP-based pharmaceuticals, chemical modification of RNAi molecules, and RNAi drugs and processes directed at particular disease indications.

We have filed many patent applications with the European Patent Office that have been granted. In Europe, upon grant, a period of nine months is allowed for notification of opposition to such granted patents. If our patents are subjected to interference or opposition proceedings, we would incur significant costs to defend them. Further, our failure to prevail in any such proceedings could limit the patent protection available to our RNAi platform, including our product candidates.

Tekmira has a portfolio of approximately 95 patent families, in the U.S. and abroad, that are directed to various aspects of LNPs and LNP formulations. The portfolio includes approximately 72 issued U.S. patents, approximately 71 issued non-U.S. patents, and



approximately 229 pending patent applications, including the following patents and applications in the United States and Europe<sup>(1)</sup>:

Invention Category	Title	Priority Filing Date*	Status**	Expiration Date***
LNP	Lipid Encapsulated Interfering RNA	07/16/2003	U.S. Pat. No.7,982,027; application pending in Europe	07/16/2024
LNP	Lipid Encapsulated Interfering RNA	06/07/2004	U.S. Pat. No. 7,799,565; European Pat. No.1766035	06/07/2025
LNP	Novel Lipid Formulations for Nucleic Acid Delivery	04/15/2008	U.S. Pat. No. 8,058,069; application pending in Europe	04/15/2029
LNP	Novel Lipid Formulations for Delivery of Therapeutic Agents to Solid Tumors	07/01/2009	U.S. Pat. No.8,283,333 Applications pending in U.S. and Europe	06/30/2030
LNP Manufacturi	<b>ng</b> Liposomal Apparatus and Manufacturing Methods	06/28/2002	U.S. Pat. No. 7,901,708; European Pat. No. 1519714	06/28/2023
LNP Manufacturi	ngSystems and Methods for Manufacturing Liposome	es 07/27/2005	Application pending in U.S. and Europe	07/27/2026
Novel Lipids	Cationic Lipids and Methods of Use	06/07/2004	U.S. Pat. No. 7,745,651; European Pat. No. 1781593	06/07/2025
Novel Lipids	Polyethyleneglycol-Modified Lipid Compounds an Uses Thereof	d 09/15/2003	U.S. Pat. No. 7,803,397; European Pat. No. 1664316	09/15/2024
Novel Lipids	Improved Cationic Lipids and Methods for the Delivery of Therapeutic Agents	07/01/2009	Application pending in the U.S.	06/30/2030
Chemical Modifications	Modified siRNA Molecules and Uses Thereof	11/02/2005	U.S. Pat. Nos. 8,101,741 and 8,188,263 ; applications pending in Europe and U.S.	11/02/2026
Chemical Modifications	Modified siRNA Molecules and Uses Thereof	06/09/2006	U.S. Pat. No. 7,915,399	06/08/2027
Therapeutic Target	siRNA Silencing of Apolipoprotein B	11/17/2004	Applications pending in U.S. and Europe	11/17/2025
Therapeutic Target	Compositions and Methods for Silencing Apolipoprotein B	07/01/2009	U.S. Pat. No. 8,236,943 Application pending in Europe	06/30/2030
Therapeutic Target	siRNA Silencing of Filovirus Gene Expression	10/20/2005	U.S. Pat. No. 7,838,658	10/20/2026
Therapeutic Target	Compositions and Methods for Silencing Ebola Virus Gene Expression	07/20/2009	Application pending in U.S.	07/20/2030
Therapeutic Target	Silencing of Polo-Like Kinase Expression using Interfering RNA	12/27/2007	Applications pending in U.S. and Europe	12/27/2028

(1) Patent information current as of December 31, 2012.



- \* Priority filing dates are based on the filing dates of provisional patent applications. Provisional applications expire unless they are converted to nonprovisional applications within one year.
- \*\* An "allowed" patent application is an active case that has been found by the patent office to contain patentable subject matter, subject to the payment of issue/grant fees by the applicant.
- \*\*\* Once issued, the term of a US patent first filed after mid-1995 generally extends until the 20th anniversary of the filing date of the first nonprovisional application to which such patent claims priority. It is important to note, however, that the United States Patent & Trademark Office, or USPTO, sometimes requires the filing of a Terminal Disclaimer during prosecution, which may shorten the term of the patent. On the other hand, certain patent term adjustments may be available based on USPTO delays during prosecution. Similarly, in the pharmaceutical area, certain patent term extensions may be available based on the history of the drug in clinical trials. We cannot predict whether or not any such adjustments or extensions will be available or the length of any such adjustments or extensions.