



Initiating Coverage Report

# **RXi Pharmaceuticals**

# Building leadership in RNAi and Immunotherapy



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### Date: 17 May 2017

Name:	RXi Pharmaceuticals
Country:	United States
Price:	USD 0.59
ISIN Code:	US74979C501
Reuters Code:	RXII
Market Cap (USD m):	13.0
EV (USD m):	0.0
Cash & cash eq. (USD m):	13.0
Shares outstanding (m):	22.1
Volume:	969,198
Free float:	64%
52-week Range:	0.51-3.27

USD m	2014A	2015A	2016A
Total Revenues	0.0	0.0	0.0
Net (Loss)/Profit	(8.800)	(10.223)	(8.994)
Net loss p.s. (cents)	(7.90)	(2.10)	(1.64)
R&D costs	5.680	6.925	5.415
Cash increase/(decrease)	(2.894)	(3.379)	7.789
Cash and market sec.	8.496	5.117	12.906



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# **Executive Summary**

• RXi Pharmaceuticals is a clinical stage RNAi company developing innovative therapeutics based on its self-delivering RNAi (sd-rxRNA®) platform. Building on the pioneering discovery of RNAi, scientists at RXi have harnessed the naturally occurring RNAi process which has the ability to "silence" or down-regulate the expression of a specific gene that may be overexpressed in a disease condition. RXi developed a robust RNAi therapeutic platform including self-delivering RNA (sd-rxRNA®) compounds, that have the ability to highly selectively block the expression of any target in the genome, thus providing applicability to many therapeutic areas. Current clinical programs include dermatology and ophthalmology. The Company is also developing a small molecule, Samcyprone™, which is currently being evaluated in Phase II clinical trials for the treatment of cutaneous warts.

FURANCIAL COSTDUCTE ON LIFE SEVENCES

- At the beginning of this year the company concluded the acquisition of private biotech company Mirlmmune which expands RXi's pipeline to include cell-based immunotherapy to treat cancer. Mirlmmune had been focused on the development of next generation immunotherapies for the treatment of cancer. Mirlmmune combined two leading approaches to cancer treatment: immune checkpoint inhibition and cell-based immunotherapies. Mirlmmune already had an exclusive license to utilize RXi's proprietary sd-rxRNA technology for use ex vivo treatment of cell-based cancer immunotherapies.
- Using RXi's sd-rxRNA technology, Mirlmmune demonstrated in vitro that multiple sd-rxRNA compounds can be used alone or in combination to target and silence extracellular, as well as intracellular, checkpoints in immune cells. Additional in vitro data demonstrated that PD-1 silencing by sd-rxRNA in patient-derived tumor infiltrating lymphocytes (TILs) resulted in enhanced killing of melanoma tumor cells from the same patient in culture. Mirlmmune has also shown in a mouse model of human ovarian cancer that in vivo treatment with mesothelin CAR T-cells transfected with a PD-1 targeting sd-rxRNA significantly reduced the rate of tumor growth as compared to vehicle control



- The Company's lead product candidate and first RNAi clinical product candidate, RXI-109, is a selfdelivering RNAi compound. RXI-109 is currently being evaluated in a Phase II clinical trial, Study 1402, to prevent or reduce dermal scarring following scar revision surgery of an existing hypertrophic scar and in a Phase I/II clinical trial, Study 1501, to evaluate the safety and clinical activity of RXI-109 to prevent the progression of retinal scarring in subjects with wet age-related macular degeneration ("AMD").
- The market potential for RXi's products in development is large. Scarring represents a high unmet medical need as there are currently no FDA approved therapies for the treatment and prevention of scars in the skin. Despite a significant unmet need, no clinically-proven prescription anti-scarring treatment is available on the market today. In the U.S. alone, the estimated market potential for an effective anti-scarring treatment is over USD 4 billion annually. If approved, RXI-109 could be a "first-in-class" RNAi treatment for the prevention or reduction of post-surgical dermal scarring.
- End of last year, the company successfully raised USD 11.5 million from an underwritten public offering. After the raise, the Company's current cash position is USD 13.0 million, and we believe that this should be sufficient to carry out the further development of its pipeline in the coming 12-18 months. RXi plans to use the net proceeds to support the company's clinical trials, to support general corporate purposes and to finance the integration of Mirlmmune and the development of its pipeline.
- Based on our NPV valuation, we believe that RXi Pharmaceuticals is substantially undervalued at the current share price of USD 0.59. We have increased our valuation to USD 100-125 million or USD 4.50-5.50 per share from USD 75-100 million or USD 3.50-4.50 per share due to the fact that we have increased our LOA and market potential for RXi's lead product RXI-109



# **Company Profile & Technology**

RXi Pharmaceuticals is a clinical-stage RNAi company developing innovative therapeutics that address unmet medical needs. The Company's development programs are based on its proprietary self-delivering RNAi (sd-rxRNA®) platform and Samcyprone<sup>™</sup>, a small molecule that is a proprietary ointment formulation of diphenylcyclopropenone (DPCP). Its clinical development programs include RXI-109, an sd-rxRNA for the treatment of dermal and ocular scarring, and Samcyprone<sup>™</sup>, for the treatment of such disorders as warts, alopecia areata, non-malignant skin tumors and cutaneous metastases of melanoma. Beginning of 2017, RXi concluded the acquisition of Mirlmmune, a privately-held company focused on the development of next generation immunotherapies for the treatment of cancer. Mirlmmune combined two leading approaches to cancer treatment: immune checkpoint inhibition and cell-based immunotherapies.

Drug delivery has been the primary challenge in developing RNAi therapeutics since its initial discovery. One conventional solution to the delivery problem involves encapsulation into a lipid-based particle, such as a liposome, to improve circulation time and cellular uptake. Scientists at RXi have used an alternative approach to delivery in which drug-like properties were built into the RNAi compound itself. These novel compounds are termed 'self-delivering' RNAi compounds or sd-rxRNA. In preclinical studies RXi has demonstrated efficient cellular uptake of sd-rxRNA in tissues such as skin, retina, spinal cord and liver. In March 2015, RXi out-licensed the sd-rxRNA technology to Mirlmmune specifically for ex vivo use in developing cell-based cancer immunotherapies, signifying validation of RXI's technology platform and paving the way for similar future agreements.

#### RNAi Technology: One of the Major Breakthroughs in Modern Biology

RNA Interference (RNAi) is one of the most important technological breakthroughs in modern biology, allowing us to directly observe the effects of the loss of function of specific genes in mammalian systems. It represents a breakthrough in understanding how genes are turned on and



off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today. Fire and Mello won the 2006 Nobel Prize in Physiology or Medicine for their discovery of RNA interference.



RNAi is a natural mechanism for silencing specific genes present in all multicellular organisms. Genes provide cells with the instructions for making proteins, and proteins — or more specifically defective proteins — are the cause of a large number of human diseases. When a gene is silenced by RNAi, the mRNA coding for the targeted protein is reduced, thus decreasing the cell's ability to make the protein encoded by that gene, thereby reducing the occurrence of the associated disease. Viral infections are important potential targets for RNAi-based therapies. Reducing the activity of key viral genes can cripple the virus, and numerous studies have already hinted at the promise of RNAi for treating viral infections. In laboratory-grown human cells, investigators have stopped the growth of HIV, polio, hepatitis C, Ebola and other viruses using this approach.



The strength of RNAi as a research tool will also have an enormous potential impact on medicine. Knocking down a gene's activity yields a wealth of information about its functions in cellular pathways. Prior to the discovery of RNAi, the process was laborious and could take months. In the early 1990s, a number of scientists observed independently that RNA inhibited protein expression in plants and fungi. This phenomenon, identified but not understood, was then known as "post transcriptional gene silencing" and "quelling". In 1998 Fire and Mello observed in Caenorhabditis (C.) elegans that double-stranded RNA (dsRNA) was the source of sequence-specific inhibition of protein expression, which they called "RNA interference". While the studies in C. elegans were encouraging at that time the use of RNAi as a tool was limited to lower organisms because delivering long dsRNA for RNAi was nonspecifically inhibitory in mammalian cells.

#### RXi's Proprietary RNAi Platform: sd-rxRNA

A successful RNAi therapeutic platform includes stable, specific and potent RNAi compounds and the ability to deliver these compounds to the tissue(s) of choice. One conventional solution to the delivery problem involves encapsulation into a lipid-based particle, such as a liposome, to improve circulation time and cellular uptake. Scientists at RXi have used an alternative approach to delivery in which drug-like properties were built into the RNAi compound itself. These novel compounds are termed 'self-delivering' RNAi compounds or sd-rxRNA. The proprietary combination of chemical modifications that results in spontaneous cellular uptake of sd-rxRNA without the need for a delivery vehicle was discovered through systematic medicinal chemistry screening. sd-rxRNAs are hybrid oligonucleotide compounds that RXi believes combine the beneficial properties of both conventional RNAi and antisense technologies.

Traditional, single-stranded antisense compounds have favorable tissue distribution and cellular uptake properties. However, they do not have the intracellular potency that is a hallmark of double-stranded RNAi compounds. Conversely, the duplex structure and hydrophilic character of traditional RNAi compounds results in poor tissue distribution and cellular uptake. In an attempt to combine the best properties of both technologies, sd-rxRNA has a single-stranded



phosphorothioate region, a short duplex region, and contains a variety of nuclease-stabilizing and lipophilic chemical modifications. The combination of these features allows sd-rxRNA to achieve efficient spontaneous cellular uptake and potent, long-lasting intracellular activity. RXi's sd-rxRNA compounds are designed for therapeutic use and have drug-like properties, such as high potency, target specificity, serum stability, reduced immune response activation, and efficient cellular uptake.

In order for a gene to guide the production of a protein, it must first be copied into a singlestranded chemical messenger (messenger RNA or mRNA), which is then translated into protein. Abnormal expression of certain genes (too much or too little) can result in disease, as can expression of an abnormal protein from a gene with a mutation.





RNA interference (RNAi) is a naturally occurring process by which a particular mRNA can be destroyed before it is translated into protein. The process of RNAi can be artificially induced by introducing a small double-stranded fragment of RNA that corresponds to a particular mRNA into a cell. A protein complex within the cell called RISC (RNA-Induced Silencing Complex) recognizes



this double-stranded RNA fragment and uses one strand, the guide strand, to bind to and destroy its corresponding cellular mRNA target. If the mRNA is destroyed in this way, the encoded protein cannot be made. Thus, RNAi provides a way to potentially block the expression of specific proteins. Since the overexpression of certain proteins plays a role in many diseases, the ability to inhibit gene expression with RNAi provides a potentially powerful tool to treat human disease.

The sequence of the entire human genome is now known, and the mRNA coding sequence for many proteins is already available. Supported by numerous gene-silencing reports and our own research, we believe that this sequence information can be used to design RNAi compounds to interfere with the expression of almost any specific gene. We also believe that the Company's RNAi platform may allow us to develop therapeutics with significant potential advantages over traditional drugs. These advantages include:

- High specificity for targeted genes;
- High potency (low doses);
- Ability to interfere with the expression of potentially any gene;
- Accelerated generation of lead compounds; and
- Low toxicity, natural mechanism of action.



# RXi Enters Immunotherapy with the acquisition of MirImmune

Late 2016, RXi announced that it entered into an exclusive option agreement to acquire Mirlmmune, for a share amount equal to 19.99% of the RXi common stock outstanding at the time of the close, plus certain undisclosed milestones. Already in the beginning of 2015, RXi had granted an exclusive license to Mirlmmune to utilize the Company's novel and proprietary sd-rxRNA technology for use treatment of ex vivo cell-based cancer immunotherapies. Mirlmmune has been focusing on immune checkpoint modulation since its inception in 2014.

Immune Checkpoint Modulators block the ability of certain proteins, called immune checkpoint proteins, to limit the strength and duration of immune responses. These proteins normally keep immune responses in check by preventing overly intense responses that might damage normal cells as well as abnormal cells. But, researchers have learned that tumors can commandeer these proteins and use them to suppress immune responses. PD-1 is an example of an Immune Checkpoint, others include CTLA-4, TIM3 and LAG-3.

Unlike other immunotherapies or cancer vaccines that work by strengthening the immune system or training it to attack tumor cells, checkpoint inhibitors work to defeat a cancer resistance mechanism that causes immune cells to see tumor cells as "self". Once this veil or "brake" is lifted, the immune response may be enough to defeat the cancer cells on its own, but a wide ranging array of therapeutic combinations is being tested. Blocking the activity of immune checkpoint proteins releases the "brakes" on the immune system, increasing its ability to destroy cancer cells. Several immune checkpoint inhibitors have been approved by the FDA. The first such drug to receive approval, ipilimumab (Yervoy®), for the treatment of advanced melanoma, is an antibody that blocks the activity of a checkpoint protein known as CTLA4, which is expressed on the surface of activated immune cells called cytotoxic T lymphocytes. CTLA4 acts as a "switch" to inactivate these T cells, thereby reducing the strength of immune responses; ipilimumab binds to CTLA4 and prevents it from sending its inhibitory signal.



Since licensing RXi's technology, Mirlmmune has identified lead compounds against six different extracellular and intracellular immune checkpoints including PD-1 and CTLA-4. It also demonstrated the silencing of all six targets by these compounds in in vitro studies both singly and in combination. The ability to simultaneously silence multiple checkpoint genes and to target intracellular targets that antibodies cannot reach could be a competitive advantage of the technology.



Using RXi's sd-rxRNA technology, Mirlmmune demonstrated in vitro that multiple sd-rxRNA compounds can be used alone or in combination to target and silence extracellular, as well as intracellular, checkpoints in immune cells. The use of this technology ex vivo could be included as part of existing cell treatment protocols essential for all therapeutic cells such as CART. Additional in vitro data demonstrated that PD-1 silencing by sd-rxRNA in patient-derived tumor infiltrating lymphocytes (TILs) resulted in enhanced killing of melanoma tumor cells from the same patient in culture. Mirlmmune has also shown in a mouse model of human ovarian cancer that in



vivo treatment with mesothelin CAR T-cells transfected with a PD-1 targeting sd-rxRNA significantly reduced the rate of tumor growth as compared to vehicle control. Furthermore, the silencing of PD-1 in the CAR T-cells isolated from these tumors persisted for at least one month. End of last year, MirImmune provided new data demonstrating silencing of a number of undisclosed immunosuppressive targets in natural killer cells (NK cells) using RXi's sd-rxRNA compounds. This adds to a remarkable set of immune checkpoint modulation studies in human T-cells, including CAR T-cells and TILs. In most cell types, the sd-rxRNA treatment results in potent silencing while maintaining close to 100% transfection efficiency and nearly full cell viability. Moreover, the silencing effect has been validated in a number of clinically used cell treatment protocols.

Several researchers estimate that the market for immunotherapeutic approaches in cancer treatment is expected to exceed USD 30 billion by 2023, driven by novel agents, combination therapy, longer treatment times and the emergence of predictive Biomarkers. Within cancer immunotherapy, immune checkpoint inhibitors are taking the bulk of the market with and expected CAGR more than 50%. See also the graph below.

The growth is driven by:

- High adoption rates in Western countries, given immunotherapies have a largely welltolerated adverse event profile compared with conventional chemotherapy;
- Immunotherapy treatment months/patient to likely materially expand due to improved progression free survival (PFS) associated with immunotherapy, multiple lines of therapy during a patient's disease and maintenance usage;
- Likely use of repeat immunotherapy based approach in patients who lose their partial response, given well tolerated adverse event profile and mechanistic rationale;





Source: DR/Decision Resources LLC



# **Clinical Overview RXi Pipeline**

RXi's pipeline is focused on the following areas: dermatology, including cosmetic product development, ophthalmology and cell-based cancer immunotherapy. Its RNAi therapies are designed to "silence," or down-regulate, the expression of a specific gene that may be over-expressed in a disease condition and its immunotherapy agents will treat diseases by inducing or enhancing an immune response.



Source: RXi Pharmaceuticals

#### RXI-109: Novel treatment in scarring

The Company's lead product candidate and first RNAi clinical product candidate, RXI-109, is a selfdelivering RNAi compound (sd-rxRNA) that started clinical trials in 2012. RXI-109 is designed to reduce the expression of connective tissue growth factor ("CTGF"), a critical regulator of several biological pathways involved in fibrosis, including scar formation in the skin and eye.



CTGF is an extracellular matrix protein that plays a key role in tissue regeneration and repair. During wound healing, CTGF modulates signals from a wide range of factors in the cell and in this way controls critical cellular pathways including scar tissue deposition and remodeling. CTGF is involved in the differentiation of fibroblasts to contractile myofibroblasts which are the main cells responsible the deposition of collagen, a major structural protein of a scar. Elevated levels of CTGF-dependent signaling can prolong the tissue repair process and lead to pathological scarring, fibrosis, and cancer.



RXI-109 is currently being evaluated in a Phase II clinical trial, Study 1402, to prevent or reduce dermal scarring following scar revision surgery of an existing hypertrophic scar and a Phase I/II clinical trial, Study 1501, to evaluate the safety and clinical activity of RXI-109 to prevent the progression of retinal scarring in subjects with wet age-related macular degeneration ("AMD").



In December 2016, the Company announced that preliminary data from the first two cohorts from Study 1402 confirmed the positive differentiation of hypertrophic scars from untreated surgery incisions in subjects treated with 5 mg/cm of RXI-109 over 3 months. The data included review of the post-treatment follow-up period through 9 months post-surgery. RXI-109 was safe and well tolerated. Additionally, as expected, limited 3-month data available from a third Cohort appear to align with that of the first two cohorts as these subjects all had the same dosing schedule through month 3. A complete read-out of the whole study, including all four cohorts with follow-up until 9 months post-surgery, is expected in 2017H2.



Blinded panel was asked: Scar A looks better? Scar B looks better? or Not different?

Observed differences at 3 months continue to be observed through month 9 (6 months post last dose)

Source: RXi Pharmaceuticals

Study 1501 is a multi-dose, dose escalation study conducted in subjects with AMD with evidence of subretinal fibrosis. Each subject will receive four doses of RXI-109 by intraocular injection at one month intervals for a total dosing period of three months. The safety and tolerability of RXI-109, as well as the potential for clinical activity, will be evaluated over the course of the study using numerous assessments to monitor the health in the retina and to assess visual acuity. The first two cohorts in Study 1501 are completely enrolled and dosing in the third cohort at the



highest planned dose level has begun. To date there have been no safety issues that precluded continuation of dosing. Complete enrollment is anticipated for 2017H1 with a complete safety read out of the study in 2017H2.

Currently, there is no effective way to prevent the formation or progression of retinal scars that may occur as a consequence of the number of debilitating ocular diseases. In advanced neovascular or wet-AMD, the Company's first area of study, retinal scarring can result in continued vision loss even if the patient is being treated with an anti-vascular endothelial growth factor ("VEGF") therapy. RXI-109 has the potential to fill this unmet medical need by reducing this continuing damage to the retina and in doing so help preserve these patients' vision for a longer period of time.

#### Samcyprone<sup>™</sup>: Warts

In December 2014, the Company broadened its clinical pipeline with an exclusive, global license to Samcyprone<sup>™</sup>, RXi's second clinical candidate. Samcyprone<sup>™</sup> is a proprietary topical formulation of the small molecule diphenylcyclopropenone ("DPCP"), an immunomodulator that works by initiating a T-cell response. The use of Samcyprone™ allows sensitization using much lower concentrations of DPCP than are used with existing compounded DPCP solutions, avoiding hyper-sensitization to subsequent challenge doses. DPCP, the active ingredient in Samcyprone™, has long been used to treat warts and has also been used for several other indications, such as to stimulate hair re-growth in alopecia areata and to clear cutaneous metastases of melanoma. In March 2015, the FDA granted Orphan Drug Designation to the Company for Samcyprone™ for the treatment of malignant melanoma stage IIb to IV. Samcyprone™ is currently being evaluated in a Phase IIa clinical trial, Study 1502, for the clearance of common warts. Study 1502 was initiated in December 2015. In December 2016, the Company announced the results from a preliminary review of sensitization and wart clearance data from a subset subjects that have completed the 10 week treatment phase of Study 1502. Results showed that greater than 90% of the subjects demonstrated a sensitization response, a prerequisite to be able to develop a therapeutic response. Additionally, more than 60% of the subjects responded to the treatment by exhibiting either complete or greater than 50% clearance of all treated warts with up to 10 weekly treatments. Samcyprone<sup>™</sup> treatment has been generally safe and well tolerated with expected drug-related

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adverse events being local reactions due to the sensitization and challenge responses in the skin. The complete readout of the final study is anticipated in the 2017H2.

#### Immuno-oncology Cell Therapies (previously MirImmune)

Mirlmmune's approach builds on current immunotherapy approaches, but provides some key advantages. One major advantage is that pretreatment with Mirlmmune's targeted compounds allow multiple immune checkpoints to be attenuated within the same therapeutic cell; an improvement which could dramatically increase their tumor cell killing capability. In addition, these therapeutic immune cells may lack some known side effects associated with the checkpoint inhibitor toxicity while potentially improving efficacy over current immunotherapy approaches. Using RXi's sd-rxRNA technology, Mirlmmune demonstrated in vitro that multiple sd-rxRNA compounds can be used alone or in combination to target and silence extracellular, as well as intracellular, checkpoints in immune cells. Additional in vitro data demonstrated that PD-1 silencing by sd-rxRNA in patient-derived tumor infiltrating lymphocytes (TILs) resulted in enhanced killing of melanoma tumor cells from the same patient in culture. Mirlmmune has also shown in a mouse model of human ovarian cancer that in vivo treatment with mesothelin CAR T-cells transfected with a PD-1 targeting sd-rxRNA significantly reduced the rate of tumor growth as compared to vehicle control. Furthermore, the silencing of PD-1 in the CAR T-cells isolated from these tumors persisted for at least one month.

In December 2016, Mirlmmune provided new data demonstrating silencing of a number of undisclosed immunosuppressive targets in natural killer cells (NK cells) using RXi's sd-rxRNA compounds. This adds to a remarkable set of immune checkpoint modulation studies in human T-cells, including CAR-T cells and tumor Infiltrating lymphocytes (TILs). In most cell types, the sd-rxRNA treatment results in potent silencing while maintaining close to 100% transfection efficiency and nearly full cell viability. Moreover, the silencing effect has been validated in a number of clinically used cell treatment protocols.



# SWOT Analysis

Strengths	Weaknesses
Strong management with extensive relevant	Operating losses cumulating year-on-year
technical, commercial and financial expertise	
Clinical stage pipeline in a disease with a relatively	Relatively low market value makes its more
high prevalence	challenging to be on investor's radar.
Opportunities	Threats
Ageing population offers predictable and ongoing	Increasing competition from larger companies
strong growth in number of patients	
Large growing markets	Failure to sign partnerships in key markets
Increasing presence in immune oncology with the	
acquisition of Mirlimmune, thereby profiting from	
high expected growth in immune checkpoint	
stimulators and immune therapy	



### **Patent Position**

RXi Pharma's intellectual property is derived through its internal research and licensing agreements. Much of its technology and many of the company's processes depend upon the knowledge, experience and skills of key scientific and technical personnel.

As of 2017, RXi Pharmaceuticals owned twenty-nine patent families covering its compounds and technologies, including RXI-109 and Samcyprone<sup>™</sup>. In total these patent families include 76 issued patents, thirteen of which cover RXi's self-delivering RNAi platform. These thirteen patents broadly cover both the composition and methods of use of its proprietary self-delivering platform technology and uses of its sd-rxRNAs targeting CTGF for the treatment of fibrotic disorders, including RXI-109 for the treatment of dermal and ocular fibrosis. These patents are scheduled to expire between 2029 and 2031.

Furthermore, there are 44 patent applications, encompassing new RNAi compounds and their use as therapeutics and/or cosmetics, chemical modifications of RNAi compounds that improve the compounds' suitability for therapeutic uses (including delivery) and compounds directed to specific targets (i.e., that address specific disease states). The patents and any patents that may issue from these pending patent applications will, if issued, be set to expire between 2022 and 2035, not including any patent term extensions that may be afforded under the Federal Food, Drug, and Cosmetic Act (and the equivalent provisions in foreign jurisdictions) for any delays incurred during the regulatory approval process relating to human drug products (or processes for making or using human drug products).

#### Patent and Patent Applications Relating to Samcyprone™

The Samcyprone<sup>™</sup> portfolio includes one issued patent and three patent applications. The patent and patent applications cover both the compositions and methods of use of Samcyprone<sup>™</sup> for the treatment of warts, human papilloma virus (HPV) skin infections, skin cancer (including melanoma) and immunocompromised patients. The patent and any patents that may issue from the pending



applications will be set to expire between 2019 and 2031, not including any patent term extensions that may be afforded under the Federal Food, Drug, and Cosmetic Act (and the equivalent provisions in foreign jurisdictions) for any delays incurred during the regulatory approval process relating to human drug products (or processed for making or using human drug products).

#### Intellectual Property License Agreements

RXi has secured exclusive and non-exclusive rights to develop therapeutics by licensing key RNAi technologies, Samcyprone<sup>™</sup> and patent rights from third parties. These rights relate to chemistry and configuration of compounds, delivery technologies of compounds to cells and therapeutic targets. As the company continues to develop its own proprietary compounds, RXi evaluates both its in-licensed portfolio as well as the field for new technologies that could be in-licensed to further enhance the intellectual property portfolio and unique position in the RNAi and immunotherapy space. In September 2011, the company entered into agreements with Advirna pursuant to which Advirna assigned its existing patent and technology rights to RXi related to sd-rxRNA technology in exchange for the agreement to issue 5% of the Company's fully-diluted shares, pay an annual maintenance fee of USD 100,000 and pay a one-time milestone payment of USD 350,000 upon the issuance of the first patent with valid claims covering the assigned technology. The common shares of the company were issued to Advirna in 2012 and the one-time milestone payment was paid in 2014. Additionally, RXi will be required to pay a 1% royalty to Advirna on any license revenue received by RXi with respect to future licensing of the assigned Advirna patent and technology rights.



### **Financials**

For 2016FY ended 31 December 2016, total net losses applicable to common stockholders amounted to USD 11.1 million compared to USD 10.4 million in the same period in the previous year. Research and development costs for the year ended December 31, 2016 was USD 5.4 million, which included USD 0.2 million of non-cash stock-based compensation expense, as compared with USD 6.9 million in 2015 including USD 0.6 million of non-cash stock-based compensation expense. The decrease in research and development expenditure was primarily due to cash and equity fees payable to Hapten Pharmaceuticals, LLC upon the close of the Samcyprone<sup>™</sup> licensing agreement and manufacturing expenses for the RXI-109 drug product, both of which occurred in 2015.

General and administrative costs for the year ended December 31, 2016 amounted to USD 3.6 million, which included USD 0.5 million of non-cash stock-based compensation expense, as compared with USD 3.3 million for 2015, which included USD 0.9 million of non-cash stock-based compensation expense. The increase in general and administrative expense year over year was primarily due to the company's focus on business development activities and an increase in legal expenses due to the company's acquisition of Mirlmmune Inc. These increases in general and administrative expenses in general and administrative expenses.

On December 21, 2016, the Company closed an underwritten public offering of 2,131,111 Class A Units, at a public offering price of USD 0.90 per unit, consisting of one share of the Company's common stock, and a five-year warrant to purchase one share of common stock at an exercise price of USD 0.90 per share and 8,082 Class B Units, at a public offering price of USD 1,000 per unit, consisting of one share of Series B convertible preferred stock, which is convertible into 1,111.11 shares of common stock, and 1,111.11 warrants. The offering included an over-allotment option for the underwriters to purchase an additional 1,666,666 Class A Units, which the underwriters fully exercised. The total net proceeds of the offering, including the exercise of the over-allotment option, was \$10.1 million after deducting all costs.



In March 2015, Mirlmmune Inc., a privately-held company focused on the development of novel immunotherapies for the treatment of cancer, entered into an exclusive license agreement for use of RXi's sd-rxRNA technology in developing innovative cell-based cancer immunotherapies. Mirlmmune's progress in cell therapy using RXi's technology formed a strong foundation for therapeutic development in the immuno-oncology space. As a result, RXi entered into an agreement to acquire Mirlmmune which was completed earlier this year.

USD million	2014A	2015A	2016A
Revenues	0.071	0.034	0.019
R&D Costs	5.680	6.925	5.415
SG&A	3.217	3.346	3.619
Operating Profit/(Loss)	(8.826)	(10.237)	(9.015)
Net Profit/(Loss)	(8,800)	(10.223)	(8.994)
Accretion of convertible preferred stock	(4.130)	(0.209)	(2.075)
Net Profit/(Loss) applicable to common stockholders	(12.930)	(10.432)	(11.069)

#### Profit & Loss Statement

#### Consolidated statement of cash flows

USD million	Dec 31 <sup>st</sup> 2015A	Dec 31 <sup>st</sup> 2016A
	(12 months)	(12 months)
Cash flow from operating activities	(7.317)	(7.760)
Cash flow from investing activities	(5.557)	5.346
Cash flow from financing activities	9.495	10.203
Cash and cash equivalents at beginning of the period	8.496	5.117
Net change in cash and cash equivalents	(3.379)	12.906



# **Management Capabilities**

RXi Pharmaceuticals is being built by seasoned biotechnology innovators. The company is led by an experienced Board and management team, which has been responsible for the development of the business and has a long term track record of developing, protecting and commercializing innovative scientific products and processes. In the past several years, the company has been investing in developing a team of experts that have a focus on patient outcomes and can deliver results. Its board and senior management team are highly experienced in the early and late stage development and commercialization of therapeutics in RNAi.

#### Management Team

#### Geert Cauwenbergh Dr.Med.Sc, President and Chief Executive Officer

Dr. Cauwenbergh was appointed President and Chief Executive Officer of RXi Pharmaceuticals Corporation in April of 2012. Prior to joining RXi, Dr. Cauwenbergh served as Chairman and Chief Executive Officer of Barrier Therapeutics, Inc., a publicly-traded biopharmaceutical company he founded in 2001 that focused on dermatology drug development. Barrier was acquired by Stiefel Laboratories, Inc. in 2008. Prior to founding Barrier, Dr. Cauwenbergh held a number of ascending senior management positions at Johnson & Johnson, where he was employed for 23 years. As Vice President, Research and Development for Johnson & Johnson's Skin Research Center, he was responsible for the worldwide research and development of all skin care products for the Johnson & Johnson consumer companies. He is a member of the board of directors of Phosphagenics, Moberg Pharma and Cutanea Life Sciences. In 2005, Dr. Cauwenbergh was inducted into the New Jersey High-Tech Hall of Fame, and, from 2009 to 2010, he served as Chairman of the Board of Trustees of BioNJ. He has authored more than 100 publications and has been a guest editor for a number of books in mycology and infectious diseases. Dr. Cauwenbergh received his Doctorate in Medical



Sciences from the Catholic University of Leuven, Faculty of Medicine (Belgium), where he also completed his masters and undergraduate work.

#### Alexey Eliseev, Ph.D., Chief Business Officer

Dr. Eliseev was appointed Chief Business Officer in January 2017 to spearhead the business development initiatives for the Company's immunotherapy program. Dr. Eliseev is a highly accomplished leader with over 20 years of experience in academia, biotechnology industry and venture capital and most recently was the founder and CEO of Mirlmmune Inc. He also co-founded Therascope, later Alantos Pharmaceuticals, with a number of prominent founders including French Nobel Laureate Jean-Marie Lehn, where he later became CTO of the company and President of its US division. Alantos was acquired by Amgen in 2007. Dr. Eliseev was also among the founders of AC Immune (Switzerland) and Boston BioCom LLC. Over recent years, he has worked with Maxwell Biotech Venture Fund as its Managing Director and ran the investment activity of the fund in the United States. Dr. Eliseev earned his PhD in Bioorganic Chemistry from Moscow State University and MBA from the MIT Sloan School of Management. Following postdoctoral research in Germany and in the US, he joined the faculty at SUNY Buffalo in 1995 where he was awarded tenure in 2000.

#### Gerrit Dispersyn, Dr.Med. Sc., Chief Development Officer

Effective April 24, 2017, Dr. Gerrit Dispersyn became RXi's new Chief Development Officer. Dr. Dispersyn is an accomplished leader in clinical, product and business development. He most recently served as the Vice President, Global Head of Clinical Affairs at Integra LifeSciences Corporation. In this role, Gerrit was responsible for Integra's global strategy and execution of Clinical Development, Clinical Operations and Medical Affairs projects and a member of Integra's Senior Management Leadership team, and several of the company's core teams for M&A projects. Dr. Dispersyn has also been involved in Integra's research and business activities related to Human Cells, Tissues, and Cellular and Tissue based Products (HCT/Ps), an experience that could be beneficial for RXi's newly added focus on immuno-oncology and cell therapy. Prior to that role, he was the Vice President, Product Development & Portfolio Management for Barrier Therapeutics, Inc., a pharmaceutical company focused on the development and commercialization of products

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in the field of dermatology. The company was a spin-out of Johnson & Johnson, and currently part of GlaxoSmithKline. There he led planning and implementation of all aspects of R&D operations and strategy; scientific, competitive and business intelligence; and alliance management. Dr. Dispersyn is the founder of Ingress, LLC, a consultancy company providing R&D and clinical operations support to start-up companies, supporting several pharmaceutical drug development programs. Dr. Dispersyn holds a Dr. Med. Sc. (Ph.D. in Medical Sciences), from the Faculty of Medicine, Maastricht University, Maastricht, the Netherlands, a post-graduate degree in Biomedical Imaging, and a M.Sc. in Biochemistry, both from the University of Antwerp, Belgium.

#### Karen Bulock Ph.D., Vice President Research

Dr. Bulock currently serves as Vice President Research for RXi Pharmaceuticals Corporation. She joined Galena Biopharma, Inc. in October of 2007 and served as the Associate Director of Research until April 2012. Dr. Bulock has over twenty years of experience in assay development and discovery project management. Since joining RXi in 2011, and previously while at Galena, Dr. Bulock has managed several key programs, including the discovery and preclinical development of RXI-109, RXi's first clinical candidate. Prior to joining RXi, Dr. Bulock spent several years leading assay development and screening projects to support small molecule drug discovery programs in the fields of metabolic disease and anti-infectives at CytRx Corporation and Essential Therapeutics, Inc. Dr. Bulock received a Ph.D. in Pharmacology from Yale University. Dr. Bulock has authored numerous scientific articles and is a co-inventor on four patent applications.

#### Board of Directors, Chairman: Robert Bitterman

Mr. Bitterman currently serves as the President & CEO of Cutanea Life Sciences, Inc., a wholly owned subsidiary of Maruho Company, LTD., a specialty pharma development company focused on diseased and aging skin. Mr. Bitterman has over 18 years of executive leadership experience in the pharmaceutical and biologic life science industry. Prior to Cutanea, he served as President and CEO for Isolagen, Inc., an international, public, bioscience technology company where the primary proprietary platform used human fibroblasts for soft tissue enhancement. For 10 years, Mr. Bitterman served as the President and GM of Aventis' Dermik Laboratories, a global, strategic **RXi Pharmaceuticals** 27



business unit focused on therapeutic and aesthetic dermatology development and commercialization. Prior to assuming senior operational leadership positions, Mr. Bitterman held various positions of increasing responsibility in financial and commercial capacities within Aventis S.A. Mr. Bitterman holds an A.B. degree in Economics from The College of the Holy Cross and a Master of Business Administration degree from Boston University.



## Valuation

We have increased our valuation on RXi Pharmaceuticals to USD 100-125 million or USD 4.50-5.50 per share from USD 75-100 million or USD 3.50-4.50 per share due to the fact that we have increased our LOA and market potential for RXi's lead product RXI-109. At this moment we do not address value to the preclinical programs in RXi's pipeline. This is a potential upside for the company.

#### Phase Success and Likelihood of Approval (LOA)

In estimating a value for the clinical programs at RXi Pharmaceuticals, we made use of several studies that were done on the clinical development success rates for investigational drugs to measure success rates for investigational drugs. We analyzed individual drug program phase transitions from January 1, 2006 to December 31, 2015. For the ten years studied, 9,985 transitions in the Biomedtracker database were analyzed. A phase transition is the movement out of a clinical phase – for example, advancing from Phase I to Phase II development, or being suspended after completion of Phase I development. These transitions occurred in 7,455 clinical drug development programs, across 1,103 companies (both large and small), making this the largest study of its kind. With this broad set of data, we aimed to capture the diversity in drug development across levels of novelty, molecular modalities, and disease indications. Only company-sponsored, FDA registration-enabling development programs were considered; investigator-sponsored studies were excluded from this analysis.

The Phase I transition success rate was 63.2% (n=3,582). As this Phase is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, it is common for this phase to have the highest success rate among the clinical phases across most categories analyzed in this report. Phase I success rates may also benefit from delayed reporting bias, as some larger companies may not deem failed Phase I programs as material and thereby not report them in the public domain. The Phase II transition success rate (30.7%, n=3,862) was substantially lower than Phase I, and the lowest of the four phases studied. As this is generally the first stage, where

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proof-of-concept is deliberately tested in human subjects, Phase II consistently had the lowest success rate of all phases. This is also the point in development where industry must decide whether to pursue the large, expensive Phase III studies and may decide to terminate development for multiple reasons including commercial viability. The second-lowest phase transition success rate was found in Phase III (58.1%, n=1,491). This is significant as most company-sponsored Phase III trials are the longest and most expensive trials to conduct. The probability of FDA approval after submitting a New Drug Application (NDA) or Biologic License Application (BLA), taking into account re-submissions, was 85.3% (n=1,050). Multiplying these individual phase components to obtain the compound probability of progressing from Phase I to U.S. FDA approval (LOA) reveals that only 9.6% (n=9,985) of drug development programs successfully make it to market (see graph below)



Source: BIO Industry Analysis

Major disease areas were segmented according to the convention used by Biomedtracker, and categorized 21 major diseases and 558 indications for the 2006-2015 timeframe. As can be seen in the graphs below, there is a wide range of Likelihood of Approval (LOA) from Phase I, II and III.







#### Valuation RXI-109 in Dermal Scarring

In estimating a value for RXI-109 in dermal scarring we made use of a potential market of 200,000 scar revision surgeries in the US and 250,000 in Europe. In addition to cosmetic and reconstructive surgeries, medical interventions which could incorporate an anti-scarring agent include treatment of scarring that results from trauma, surgery or burns (especially relating to raised or hypertrophic



scarring or contracture scarring), and surgical revision of existing unsatisfactory scars. Moreover, there are over 42 million medical procedures in the U.S. each year that could potentially benefit from a therapeutic treatment that could successfully reduce or prevent scarring; thus, the market potential is quite large. We estimate a market launch in the US in 2021 and 2022 in the EU. We calculate a Risk adjusted Discount Rate of 12%. Pricing per treatment is set at USD 4,000. We estimate that RXi will partner RXI-109 in Phase III for an estimated royalty of 20%. We estimate that a peak market share of 10% is possible. This leads to a total valuation of USD 21 million or USD 0.95 per share.

#### Valuation RXI-109 in Retinal Scarring

In estimating a value for RXI-109 in retinal scarring we made use of a potential market for advanced or neovascular AMD of 1.2 million patients in the US and 1.5 million in Europe. According to the National Eye Institute, in 2010 approximately 2.07 million people had advanced AMD. The National Eye Institute further states that as the proportion of people in the U.S. age 65 and older grows larger, more people are developing age-related diseases, such as AMD. Due to the aging population, this number is expected to double to an estimated 5.44 million people in the year 2050. There is no cure for AMD and over 50% of advanced AMD patients start to develop scarring after 2 years on anti-VEGF therapy, the current standard of care. This represents a large number of patients with an unmet medical need that could benefit from a therapeutic treatment that could successfully reduce or prevent scarring in the retina, and thereby improve vision loss. We estimate of 12%. Pricing per treatment is set at USD 2,500. We estimate that RXi will partner RXI-109 in Phase III for an estimated royalty of 20%. We estimate that a peak market share of 10% is possible. This leads to a total valuation of USD 63 million or USD 2.85 per share.



#### Valuation Samcyprone for Warts

In estimating a value for Samcyprone in cutaneous warts we made use of a potential market of 32 million patients in the US and 50 million in Europe. According to the BMJ (British Medical Journal) the prevalence of cutaneous viral warts in the general population is estimated to be 7-12%. Many patients present to primary care with pain and discomfort along with other concerns, such as cosmetic appearance. Although cutaneous viral warts are ubiquitous, no definitive treatment exists. Nevertheless, most warts resolve spontaneously and a large proportion of the remainder respond to simple recommended treatment. For these reasons, potential treatments must have minimal side effects and a favourable risk profile.

We estimate a market launch in the US in 2021 and 2022 in the EU. We calculate a Risk adjusted Discount Rate of 12%. Average pricing per annual treatment is set at USD 250. We estimate that RXi will partner RXI-109 in Phase III for an estimated royalty of 15%. We estimate that a peak market share of 8% is possible. This leads to a total valuation of USD 33.2 million or USD 1.50 per share.

Program	Market	LOA	Market	No of	Royalty	Risk Adj.	Per share
			share	patients		NPV (USD	(USD)
RXI-109	2021 US	24%	10%	200,000	20%	20.9	0.95
Dermal Scarring	2022 EU			250,000	20%		
RXI-109	2022 US	17%	10%	1,200,000	20%	62.8	2.85
Retinal Scarring	2023 EU			1,500,000	20%		
Samcyprone	2021 US	24%	8%	32 mln	15%	33.2	1.50
	2022 EU			50 mln	15%		
Total						116.9	5.30

#### Break down total valuation RXi Pharmaceuticals



# **Near Term Milestones**

In the past year, RXi Pharmaceuticals has already reached a number of important milestones with the development of both its lead programs and the acquisition of Mirlmmune. In the coming 6-12 months we expect a number of important milestones that can drive the stock price upwards. These are:

- $\succ$  2017Q1: Transition to include immuno-oncology research at RXi  $\checkmark$
- > 2017H1: Identify final patients for enrollment in RXI-109-1501
- 2017H1: Initiate program to evaluate reduction of cytokines involved in cytokine release syndrome
- > 2017H1: Complete enrollment in the RXI-231 consumer study
- 2017H2: Provide data on multiple checkpoint inhibiting sd-rxRNA compounds co
  - transfected in CAR T-cells in mouse models for ovarian cancer
- ➢ 2017H2: Preclinical results on use of sd-rxRNA with TILs in melanoma
- > 2017H2: Phase II study 1402 (RXI-109 hypertrophic scarring) final data read out
- 2017H2: Phase II Study 1501 (RXI-109 retinal scarring) complete subject participation
- 2017H2: Phase II Samcyprone cutaneous warts –data read out Study 1502 and possible out-licensing
- > 2017H2: RXI-231 consumer tolerance/functional performance data available
- > 2018: Enter one sd-rxRNA checkpoint inhibitor in clinical development



### **Competitive Landscape**

During examination of comparable companies, we looked at companies that have a focus on antiscarring therapies or having cell based immune therapies in clinical trials or are working in the RNAi area. Other companies currently developing anti-scarring therapies in dermatology and ophthalmology include Promedior, miRagen Therapeutics, Allergan and Sirnaomics. Other companies that are working in the RNAi area include Alnylam Pharmaceuticals, Inc., Benitec Biopharma Limited, Silence Therapeutics plc, Quark Pharmaceuticals, Arbutus Biopharma, Arrowhead Pharmaceuticals, Dicerna Pharmaceuticals and Sylentis

#### Promedior

Promedior is a clinical-stage biotechnology company pioneering the development of targeted therapeutics to treat fibrotic diseases. Fibrosis is a process that occurs in many diseases, when normal healthy tissue is replaced with scar tissue, compromising normal function and leading ultimately to organ failure. Promedior's proprietary therapeutic platform is based upon Pentraxin-2, an endogenous human protein that acts through a unique anti-fibrotic immunotherapy mechanism to activate a regulatory switch upstream in the fibrosis cascade. Promedior's drug candidates are based on Pentraxin-2, an endogenous human protein that plays an important role in regulating the response to fibrosis. PRM-151, Promedior's lead product candidate, is a recombinant form of the endogenous human innate immunity protein, pentraxin-2 (PTX-2), which is specifically active at the site of tissue damage. In August, 2015, Bristol-Myers Squibb and Promedior entered into an agreement that granted Bristol-Myers Squibb an exclusive right to acquire Promedior and gain worldwide rights to its lead asset PRM-151. Total aggregate payments to Promedior under the agreement have the potential to reach USD 1.25 billion, which includes an upfront cash payment for the right to acquire Promedior, an exercise fee payable if Bristol-Myers Squibb elects to exercise its right to acquire the company, and subsequent clinical and regulatory milestone payments.



#### miRagen Therapeutics

miRagen Therapeutics, Inc. is a clinical-stage biopharmaceutical company discovering and developing proprietary RNA-targeted therapies with a specific focus on microRNAs and their role in diseases where there is a high unmet medical need. miRagen's two lead product candidates, MRG-106 and MRG-201, are currently in Phase 1 clinical trials. miRagen's clinical product candidate for the treatment of certain cancers, MRG-106, is an inhibitor of microRNA-155, which is found at abnormally high levels in several blood cancers. miRagen's clinical product candidate for the treatment of pathological fibrosis, MRG-201, is a replacement for miR-29, which is found at abnormally low levels in several pathological fibrotic conditions, including cardiac, renal, hepatic, and pulmonary fibrosis, as well as systemic sclerosis.

#### Sirnaomics

Sirnaomics is a biopharmaceutical company discovering and developing novel targeted therapeutics for critical human diseases by using RNA interference (RNAi) technology. The company was founded in early 2007 with the mission of advancing RNAi technology using multitargeted design of small interfering RNA (siRNA) and nanoparticle-enhanced delivery. Sirnaomics lead product candidate, STP705, is an anti-fibrosis siRNA therapeutics taking advantage of a dual-targeted inhibitory property and polypeptide nanoparticle (PNP)-enhanced delivery to directly diminish both fibrotic activity and inflammatory activity allowing for application in many disease states. STP705 is composed of two siRNA oligonucleotides, targeting TGF-β1and COX-2 mRNA respectively, and formulated in nanoparticles with Histidine-Lysine Co-Polymer (HKP) peptide. Each individual siRNA was demonstrated to inhibit the expression of their target mRNAs and combining the two siRNA's produced a synergistic effect that diminished pro-fibrogenic factors. Molecular analyses of the effects of administering the combination demonstrated that the inhibition of these targets had effects on downstream gene products associated with fibrosis including:  $\alpha$ -SMA, Col1A1, and Col3A1. Additional data suggests that reductions in TGF- $\beta$ 1 and COX-2 led to proapoptotic effects in fibroblasts. This data also suggests that STP705 has the potential for broad application in many inflammatory and fibrotic driven disease states. The route



of administration for STP705 for Scar Reduction will be via intradermal injection. A Phase IIa clinical study of STP705 for Hypertrophic Scar Treatment is awaiting commencement in the US.

#### Benitec Biopharma

Benitec Biopharma is a biotechnology company developing innovative therapeutics based on its patented gene-silencing technology called ddRNAi or 'expressed RNAi'. The company is developing ddRNAi-based therapeutics for chronic and life-threatening human conditions including hepatitis B, wet age-related macular degeneration and OPMD. Benitec has also licensed ddRNAi to other biopharmaceutical companies for applications including HIV/AIDS, Huntington's Disease, chronic neuropathic pain, cancer immunotherapy and retinitis pigmentosa. The company is also developing two ddRNAi-based therapies, one for the treatment of wet AMD, which is designated BB-AMD-211, and the other potentially for both wet and dry AMD, which is designated BB-AMD-231. The aim of this program is to develop a therapeutic that provides long-term treatment of AMD from a single intravitreal injection.

#### Silence Therapeutics

Silence Therapeutics develops a new generation of medicines by harnessing the body's natural mechanism of RNAi within its cells. Its proprietary technology can selectively inhibit any gene in the genome, specifically silencing the production of disease-causing proteins. Silence's proprietary RNA chemistries and delivery systems are designed to improve the stability of its molecules and enhance effective delivery to target cells, providing a powerful modular technology well suited to tackle life-threatening diseases.



#### Analyst: Marcel Wijma MSc

Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoeck Research (VLR) to SNS Securities in 2006, he established an award winning analyst team in biotech/life sciences at SNS Securities. In 2009, Marcel was awarded by Financial Times/Starmine as being one of the Top-3 biotech analysts in Europe. Later that year, Marcel purchased VLR from SNS Securities after which the company was reconstituted. At VLR, he leads the professional VLR research organisation, which is augmented by selected external financial researchers with a specialisation in Life Sciences. Mr. Wijma has a Masters degree in Financial Economics from Erasmus University in Rotterdam.

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