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**Initiating Coverage** 

June 19, 2014

#### **Key Metrics**

ALDX - NASDAQ	\$6.69
Pricing Date	Jun 18 2014
Price Target	\$35.00
52-Week Range	\$7.78 - \$6.00
Shares Outstanding (mm)	6.2
Market Capitalization (\$mm)	\$41.5
3-Mo Average Daily Volume	26,315
Institutional Ownership	NM
Debt/Total Capital	NM
ROE	NM
Book Value/Share	NM
Dividend Yield	NM
LTM EBITDA Margin	NM

#### EPS (\$) FY: December

	2013A	Prior 2014E	Curr. 2014E	Prior 2015E	Curr. 2015E
1Q-Mar			(0.04)A		(0.41)E
2Q-Jun			(0.53)E		(0.48)E
3Q-Sep			(0.32)E		(0.46)E
4Q-Dec			(0.36)E		(0.43)E
FY	(17.58)		(1.47)E		(1.78)E
P/E	NM		NM		NM

#### Revenue (\$M)

		Prior	Curr.	Prior	Curr.
	2013A	2014E	2014E	2015E	2015E
1Q-Mar					
2Q-Jun					
3Q-Sep					
4Q-Dec					
FY					



Source: BigCharts.com Company Description:

Aldeyra Therapeutics, Inc. (http://www.aldeyra.com/) is an emerging biotech company focusing on orphan diseases, based in Burlington, MA.

# Aldeyra Therapeutics Inc. Rating: Buy

## Aldeyra Therapeutics: Setting The Aldehyde Trap

## **Investment Highlights:**

- Initiating Coverage. We are initiating coverage on Aldeyra Therapeutics, an emerging biotechnology company focusing on the development of novel therapeutics for both rare as well as common skin and eye diseases, with a Buy rating and an 18-month price target of \$35.00 per share. In our view, Aldeyra represents an attractive opportunity in the orphan disease space, but also has the potential to leverage its technology platform to develop therapeutics for much more prevalent disorders.
- Differentiated Technology Platform. Investors should note, in our view, that Aldeyra is an example of a technology platform company founded on the basis of solid science. The firm's approach involves the discovery and development of free aldehyde trapping agents. Free aldehydes are reactive species that are known to induce inflammation and tissue damage in various contexts. Aldeyra's proprietary compounds, exemplified by the firm's lead drug candidate, NS2, specifically bind free aldehydes and drive them towards degradation in the lysosomes of cells, thus reducing inflammation and fibrosis. Therefore, in our view, these aldehyde traps have broad applicability across many disease indications and can be formulated for use in a number of settings oral administration, eye drop formulation, or topical cream-based formulation.
- Rapid Clinical Advances In The Right Indications. Aldeyra is aiming at clinical indications in which drug development can be done swiftly and cost-effectively; namely, skin and eye disorders. These diseases have the advantages of enabling rapid clinical development with short evaluation periods and readily measurable objective endpoints. Aldeyra can also expand the utility of its aldehyde traps beyond orphan indications such as Sjogren-Larsson Syndrome (SLS) and acute anterior uveitis, into much larger markets such as eczema and macular edema.
- Attractively Valued Vs. Other Orphan Drug Firms. Aldeyra is slated to begin a Phase 2 / 3 trial of its lead candidate, NS2, in SLS within the next several months. The firm trades at a market cap of roughly \$45mm, with an enterprise value of ~\$30mm. Other development-stage orphan drug companies trade at far higher valuations despite having no approved products and no Phase 3 data. Examples include Sarepta Therapeutics (SRPT/ NASDAQ, Not Rated), at \$1.3bn; Ultragenyx (RARE/NASDAQ, Not Rated), at ~\$1.4bn; and Synageva BioPharma (GEVA/NASDAQ, Not Rated), at ~\$3bn. None of these firms can pursue line extensions into non-orphan indications, whereas Aldeyra can.

## **Investment Thesis**

Aldeyra Therapeutics, Inc. (ALDX/NASDAQ) is an emerging firm focusing on treatment of rare dermatological and ophthalmological disorders. The company is a leader in the development of therapeutic approaches based on the scientific principle of free aldehyde trapping. Molecules known as free aldehydes have historically been shown to play a pivotal role in the mediation of pro-inflammatory processes, leading to toxicity and tissue damage. In our view, Aldeyra Therapeutics represents one of the few companies focusing on rare diseases that could actually leverage its lead drug candidates into larger markets. This is due to the fact that toxic free aldehyde trapping represents a broad principle with wider therapeutic implications. Aldeyra Therapeutics is also unique in that it has benefited from backing at an early stage post-inception by highly respected healthcare-focused investors, notably Domain Associates - a well-known West Coast venture capital firm - and Johnson & Johnson Development Corporation, the venture arm of Johnson & Johnson. We anticipate that Aldeyra should be able to advance its lead drug candidate, NS2, into pivotal development for the treatment of Sjögren-Larsson Syndrome (SLS) within the course of the next few months. A Phase 2 / 3 trial of a topical formulation of NS2 in SLS should report data in the second half of 2015, with a confirmatory Phase 3 study to begin later that year. Positive data from these studies should pave the way for a regulatory filing in the U.S. in early to mid-2017, with approval anticipated by the end of that year based on Priority Review status. Aldeyra is also planning to treat discoid lupus / morphea scleroderma with the same topical formulation of NS2, with Phase 2a data expected to become available in mid- to late 2015. Aldeyra plans to develop additional formulations of NS2 for SLS (oral form) and the ophthalmological disorders known as recurring acute anterior uveitis and ocular cicatricial pemphigoid (topical eye drop formulation). We believe that proof-of-concept data in uveitis and pemphigoid could be released in mid- to late 2015, along with data for the oral formulation of the drug in SLS. Accordingly, therefore, we would underscore the firm's technology platform strength, its ability to pursue multiple shots on goal, and its rapid clinical development timeline with multiple near-term value drivers as compelling reasons to consider it as an investment opportunity.

We are initiating coverage of ALDX with a Buy rating and an 18-month price target of \$35.00 per share, which assumes an enterprise value of roughly \$300 million and about nine million fully-diluted shares outstanding as of late 2015. In our view, Aldeyra represents a risk-mitigated investment opportunity priced at an attractive level. This is an orphan disease company with the ability to pursue line extensions for its lead drug candidate in additional indications that constitute much larger markets. The company's current valuation is extremely modest; it possesses an enterprise value of only \$30 million vs. enterprise values in excess of \$1 billion for other orphan disease-focused companies such as Sarepta Therapeutics (SRPT/NASDAQ, Not Rated), Synageva BioPharma (GEVA/NASDAQ, Not Rated), and Ultragenyx (RARE/NASDAQ, Not Rated). An investment in Aldeyra shares may entail above-average risk.

# **Investment Positives**

Potential For Accelerated Path To Market And Forward Integration. In our view, NS2 represents a relatively low-risk opportunity because it has a validated mechanism of action, has shown solid safety in healthy human subjects, and targets a rare disease without significant viable current treatment options. Aldeyra only needs to conduct one Phase 2/3 trial along with a single confirmatory Phase 3 trial in order to be in position to file for approval in the U.S., and approval could be secured in less than three years. In our view, Aldeyra could utilize NS2 as the platform from which to build commercial infrastructure in the U.S. market. The SLS indication could be addressed with a small sales force of 20-25 people, which is well within Aldeyra's capabilities in our view.

Attractive Technology Platform. NS2 is, in our view, an intriguing asset because of the fact that it employs the free aldehyde trapping principle to suppress inflammation and reduce tissue damage – and since it may have applicability in a broader range of indications beyond Sjögren-Larsson Syndrome (SLS). We feel that Aldeyra's technology platform should allow it to advance multiple additional therapeutic candidates into clinical development over the course of the next several years. In addition, we expect that the company will concentrate on disease indications that provide the advantages of rapid development and clinical trial outcome measures that can be readily and objectively assessed. In particular, we believe that the company is likely to focus near-term on skin and eye disorders, which largely constitute significant unmet medical needs.

**Low Current Valuation; Near-Term Value Drivers.** Aldeyra's enterprise value is ~\$30 million. The firm recently raised ~\$11 million in an Initial Public Offering (IPO) underwritten by Aegis Capital Corp., with Fidelity Investments as the anchor investor. Aldeyra could generate several substantial value drivers in the coming months, including initiation of a Phase 2 / 3 SLS study with NS2. Other orphan drug firms trade at much higher enterprise valuations (>\$1 billion), even without any products on the market.

## **Investment Risks**

**Financial Outlook.** Aldeyra Therapeutics has been unprofitable since inception and its future operational viability relies upon the successful development and commercialization of NS2 in SLS and the company's ability to generate additional positive proof-of-concept clinical data with NS2 in other indications. The firm may require additional capital within the next 12-15 months in order to finance its operations. Although Aldeyra has thus far managed to obtain sufficient capital to fund its operations, the firm may not be able to achieve this in the future. Given these factors, Aldeyra shares could experience above-average risk and volatility, in our opinion.

**FDA Unpredictability.** New therapeutics development is a multi-year process that requires human clinical trials prior to FDA approval. The amount of additional clinical data that may be required to support a regulatory filing on NS2 is unclear at this juncture, making it impossible to predict the precise timing of market entry and revenue generation. Also, review times at the FDA may take longer than originally expected.

**Competitive Landscape.** Aldeyra's products may face competitors with greater financial resources and larger marketing, sales, distribution, and service organizations. Many of the firm's competitors in the neurology domain may offer broader product lines and may have stronger relationships with specialty prescribers of neurology drugs.

**Intellectual Property.** The company relies on patents and trade secrets to protect its products from competition. The pharmaceutical industry is inherently litigious. A court might not uphold Aldeyra's intellectual property rights, or it could find that Aldeyra infringed upon another party's property rights. In addition, generics manufacturers could potentially find loopholes in Aldeyra's intellectual property estate.

**Reimbursement.** Following the institution of broad-based healthcare reform policy, reimbursement agencies have grown more wary of systematically reimbursing for drugs that are either unnecessary or provide marginal benefit at excessive cost.

**Industry risks.** The securities of emerging biotechnology and specialty pharmaceuticals companies are inherently volatile and increasingly subject to development and regulatory risk. Meeting or missing commercial milestones may result in changes in the perception of the firm and the stock price. We do not anticipate volatility to subside near-term.

For additional risk considerations, please refer to the company's SEC filings.

## **Valuation**

## Risk-Adjusted Net Present Value Analysis

We have performed a discounted cash flow analysis to determine the fair value of Aldeyra Therapeutics at this juncture. Our assessment is based on the assignment of value to four development projects at the company – the planned Phase 2 / 3 program for a topical cream-based formulation of NS2 in Sjögren-Larsson Syndrome (SLS) and the envisaged Phase 2 development of this formulation for discoid lupus; the early-stage programs for NS2 in uveitis and ocular cicatricial pemphigoid, disorders of the eye; and the firm's proprietary technology platform in the domain of free aldehyde trapping.

As shown below, we believe that the most significant near-term value driver is NS2, due to the risk-mitigated nature of the asset (proven safety and validated mechanism of action) and the orphan nature of SLS. In our view, NS2 could achieve peak sales in the U.S. market of roughly \$1.3 billion (in orphan indications only) and would have seven years of market exclusivity post-approval based on Orphan Drug status. We project pricing for NS2 starting at roughly \$125,000 per patient annually, which we believe is justifiable given the agent's orphan status. For the purposes of calculating the risk-adjusted NPV of NS2, we utilize a discount rate of 15%, a probability of success of 60% and net margins of ~80%, assuming that NS2 could be marketed in the U.S. with a sales force of 40-50 individuals. Our assumptions include a \$20 million contribution to the total rNPV for the firm from the technology platform, which we consider conservative. Investors should note that we are not currently giving Aldeyra formal credit for the potential future development of NS2 in diseases that are non-orphan in nature, such as atopic dermatitis (eczema). Such indications could prove even more lucrative overall than the orphan disorders that the company plans to pursue initially.

Table 1: Composite Net Present Value (rNPV) Analysis

NS2 Topical Formulations - Global	
Total addressable patients <sup>1</sup>	250,000
Patients seeking treatment <sup>2</sup>	100,000
Peak market share <sup>3</sup>	12%
Treatment revenue/prescription/course of therapy <sup>4</sup>	\$70,000
Peak sales <sup>5</sup>	\$1.9B
Launch <sup>6</sup>	2017 / 2018
Peak sales year	2025
Protection expires <sup>7</sup>	2026
Discount rate	15%
Probability of success <sup>8</sup>	60%
Risk-adjusted NPV <sup>9</sup>	\$280MM
NPV per share	\$30.00
Estimated Net Cash Position (\$MM; end-2015)	\$26MM
Additional Value Drivers (technology platform for free aldehyde trapping)	\$20MM
Total enterprise value	\$325MM
Shares Outstanding (MM; end-2015)	9MM
Present value-derived price target	\$35.00
Notes on assumptions:  Adult orphan skin and eye disease patients - primarily U.S. and European markets	
(Source: National Institute of Health; Centers for Disease Control and Prevention)	
<sup>2</sup> Patients likely to seek therapy (Source: Aegis Capital Corp. estimates)	
<sup>3</sup> Peak market share - blended	
<sup>4</sup> Revenue/year/patient - \$125,000 (U.S.) / \$100,000 (Europe) for cream, \$25,000 (U.S.) / \$15,000 (Europe) for eye drop; 3% annual price incre	eases
<sup>5</sup> Peak sales - treatment revenue/year x treated patients x peak market share	
<sup>6</sup> Launch in late 2017 for cream formulation / mid- to late 2018 for eye drop formulation	
<sup>7</sup> Patent expiry starting in 2026; Hatch-Waxman extensions may provide up to an additional five years of protection	
<sup>8</sup> Probability of success - validated mechanism of action; NS2 is starting Phase 2 / 3 development in Sjögren-Larsson Syndrome (SLS)	
<sup>9</sup> Cash flow fully taxed at 40% following launch; no significant net operating loss carry-forwards assumed	

## **Comparables Analysis**

Based on a comparable company analysis, it appears to us that the stock is worth approximately \$35.00 per share (see Table 2, below). This assumes that the shares trade in line with the comp group average enterprise value of roughly \$300 million and that the firm has approximately nine million shares outstanding as of late 2015. We believe that a comparison to companies in relatively late stages of clinical development is warranted, since Aldeyra has a lead candidate that is slated to enter a Phase 2 / 3 study within the next few months, and possesses a broad technology platform with the potential to yield multiple shots on goal. Accordingly, therefore, we believe that Aldeyra should be benchmarked against other companies developing therapeutics for orphan diseases.

**Table 2: Comparable Company Analysis** (Millions, Except Per-Share Data)

Development stage	Therapeutic focus	Company Name	Ticker	Rating	Closing Price (06/18/14)	Shares (MM)	Market cap (\$MM)	Cash (\$MM)	Debt (\$MM)	Enterprise value
Phase 2 / 3	Various	Auspex Pharmaceuticals	ASPX	Not Rated	\$22.54	23	513	120	14	408
Phase 2	Hematology / Orphan Diseases	Bluebird bio, Inc.	BLUE	Not Rated	\$36.66	25	899	193	0	706
Phase 3	CNS Disorders	Catalyst Pharmaceutical Partners	CPRX	Buy	\$2.39	67	161	21	0	139
Phase 3	Gastroenterology	Evoke Pharma	EVOK	Buy	\$7.77	6	47	22	3	28
Phase 1 / 2	Hepatology	Galectin Therapeutics	GALT	Buy	\$14.81	22	324	37	0	288
Phase 2b	Ophthalmology / Oncology	Lpath, Inc.	LPTN	Not Rated	\$3.83	16	60	16	0	44
Phase 2b	CNS Disorders	Opexa Therapeutics	OPXA	Buy	\$1.69	28	47	20	0	27
Phase 2 / 3	Orphan Disorders	Retrophin	RTRX	Not Rated	\$11.16	24	273	5	31	299
Phase 2 / 3	CNS Disorders	StemCells	STEM	Not Rated	\$1.57	56	87	26	16	77
Phase 2 / 3	Oncology	Stemline Therapeutics	STML	Buy	\$15.78	13	204	77	0	127
Phase 3	Gastroenterology	Synergy Pharmaceuticals	SGYP	Buy	\$4.14	94	388	71	0	317
Phase 2	Orphan Disorders	Ultragenyx	RARE	Not Rated	\$48.67	30	1462	165	0	1297
		Average					373			300
								Discre	pancy	
Current valuation	Orphan Disorders	Aldeyra Therapeutics, Inc.	ALDX	Buy	\$6.92	6	43	12	0	31
				Derived	I 18-month targ	et price				
Target valuation (18-month)	Orphan Disorders	Aldeyra Therapeutics, Inc.	ALDX	Buy	\$35.00	9	326	26	0	Projected 300

Source: First Call and Aegis Capital Corp. estimates

**Free Cash Flow:** We believe that Aldeyra Therapeutics, Inc. is likely to remain unprofitable for the foreseeable future. We utilize a discounted cash flow analysis supporting a risk-adjusted Net Present Value (rNPV) framework to derive our \$35.00 price target. This approach is described further in the next section of the report.

Our detailed analysis is split into three principal components: our discounted cash flow model, including the rNPV assessment of Aldeyra's clinical-stage development pipeline (presented in the preceding section); our assessment of the markets for Aldeyra's portfolio candidates, and the associated sales model for these drugs; and the near-term financial outlook for the company. Our historical income statement and financial projections are presented toward the back of this report.

**Taxes:** In our view, it is likely that Aldeyra Therapeutics would be able to defer tax liability for the first couple of years following the approval of its first product. However, upon the exhaustion of the net operating loss carry-forwards, we anticipate that future cash flows would likely be taxed at a 40% effective rate given the federal statutory corporate tax rate of 35% and additional state taxes that are likely to apply.

The company has incurred operating losses since inception. As of the end of 2013, the firm had net operating loss carry-forwards of approximately \$21 million. The company's net deferred tax asset may be subject to reassessment due to ownership changes, including that based on the recently-completed IPO. Furthermore, the firm believes that it may have gone through an ownership change in 2008. The net operating loss carry-forwards are currently slated to expire at various dates through 2033. If an ownership change, as defined under Internal Revenue Code 382, is judged to have occurred, the use of these carry-forwards may be subject to limitations.

# **Company Overview**

Founded in 2004, Aldeyra Therapeutics, formerly known as Aldexa Therapeutics and prior to December 2012 as Neuron Systems, Inc., is a biotech firm focused on the development of drugs for immune-mediated, inflammatory, orphan, and other diseases that are thought to be related to a naturally-occurring toxic chemical species known as free aldehydes. The firm discovered and is developing NS2, a product candidate that is designed to trap and allow for disposal of free aldehydes, for the treatment of Sjögren-Larsson Syndrome (SLS), a rare disease caused by mutations in an enzyme that metabolizes fatty aldehydes, and acute anterior uveitis, an inflammatory eye disease.

The firm believes that there is a significant unmet medical need for the therapies that it intends to develop. Currently, we are not aware of any therapy that has been approved by the FDA for the treatment of SLS. Acute anterior uveitis is often treated with corticosteroids (commonly used anti-inflammatory agents), but prolonged use of corticosteroids can lead to significant morbidity. In addition, SLS and acute anterior uveitis are rare conditions. Aldeyra intends to request Orphan Drug designation from the FDA for the drugs that it is developing to treat rare diseases.

In a variety of *in vitro* and preclinical models, NS2 has demonstrated the ability to trap free aldehydes, diminish inflammation, reduce healing time, protect key cellular constituents from aldehyde damage, and lower potential for scarring or fibrosis. Furthermore, NS2 has been tested in a variety of toxicity studies in animals and appears to be generally safe and well-tolerated. Aldeyra is also developing aldehyde traps distinct from NS2 that have the potential to treat diseases beyond SLS and uveitis. The figure below depicts the breadth of the indications in which NS2 could potentially be applied.

NS<sub>2</sub> Decreased Aldehyde Anti-Load Lipid Protection inflammatory Discoid Lupus Sjögren-Larsson Syndrome Morphea Acute Anterior Uveitis Acute Anterior Uveitis Cicatricial Pemphigoid Lesion Healing Anti-fibrotic Cicatricial Pemphigoid Cicatricial Pemphigoid Discoid Lupus Morphea Morphea Cicatricial Pemphigoid

Figure 1: Aldeyra Therapeutics Lead Candidate Target Indications

Source: Company reports

Thus far, Aldeyra has evaluated NS2 in a Phase 1 clinical trial in 48 healthy volunteers, wherein NS2 was seen to be safe and well-tolerated when given as an eye drop up to four times per day over seven days. In the second half of 2014, Aldeyra plans to initiate the following clinical trials, all of which are slated to yield data in the second half of 2015:

- A Phase 2 clinical trial with the topical NS2 eye drop in acute anterior uveitis;
- A Phase 2 / 3 clinical trial in SLS with a topical cream-based formulation of NS2

# **Background on NS2**

As shall be discussed in greater detail later in this report, free aldehydes are naturally occurring endogenous chemical species that promote inflammatory processes, among other biological pathways. At high levels, free aldehydes are toxic and have been implicated as mediators of many immune-mediated and inflammatory diseases. A variety of diseases are thought to involve free aldehydes, at least in part, including autoimmune diseases (e.g., systemic lupus erythematosis), inflammatory diseases (e.g., uveitis), neurological disease (e.g., multiple sclerosis), cardiovascular disease (e.g., atherosclerosis) and endocrinologic disease (e.g., diabetic nephropathy). Aldeyra was founded on the precept that many of these diseases constitute significant unmet medical needs and lack effective pharmacological interventions, and that interference with free aldehydes and the pathological cascades that they induce could be clinically meaningful.

NS2 is a small molecule designed specifically to trap and allow for the disposal of free aldehydes. In multiple *in vitro* and *in vivo* preclinical animal studies, NS2 appears to have minimal pharmacology, i.e., it does not appear to modify most cellular components, including most receptors, enzymes and other proteins. NS2 has been shown to bind and trap free aldehydes more rapidly than free aldehydes bind any cellular constituent. Evidence suggests that NS2 bound to aldehydes, so-called NS2-aldehyde adducts, are rapidly transported to cellular lysosomes, where the adduct is degraded within hours. Outside the lysosome, the adduct is remarkably stable, meaning that NS2-aldehyde binding is essentially irreversible in vivo, hence the notion of NS2 as an aldehyde trap. Through its essential ability to irreversibly bind free aldehydes and in essence transport the aldehydes to lysosomes for degradation, NS2 has the potential to substantially lower aldehyde levels in the human body.

Aldehyde Binding

• Aldexa's compounds rapidly trap free aldehydes and remove aldehydes from cellular constituents

• Alduct Transport

• Trapped aldehydes are transported to the lysosome

• Drug and aldehydes are metabolized within hours

Figure 2: Aldehyde Binding / Adduct Formation / Disposal Pathway

Source: Aldeyra Therapeutics, Inc.

Aside from increasing levels of inflammation, there is no generally accepted role of free aldehydes. Some physiologic molecules have aldehyde forms, including retinaldehyde (a form of Vitamin A) and pyridoxal and pyridoxal phosphate (forms of Vitamin B6), but these molecules are not "free" aldehydes, since they are tightly chaperoned and protected by special proteins. As such, retinaldehyde and pyridoxal are not exposed to the cellular milieu, thus precluding the non-specific binding characteristic of free aldehydes. Thus, aldehyde trapping is expected *a priori* only to dampen inflammatory response and, according to Aldeyra, would not be predicted to have any overt toxicity. Aldeyra has already conducted both preclinical and clinical toxicology assessment on its lead aldehyde-trapping compound, NS2, which revealed that the drug does not cause retinaldehyde or pyridoxal deficiencies. NS2 appears only to trap toxic aldehydes, and does not seem to impede the function of important physiological molecules.

Aldeyra has shown that, in mice injected with endotoxin, a single intra-peritoneal injection of NS2 – administered 30 minutes prior to endotoxin exposure – reduced levels a variety of inflammatory cytokines (protein inflammatory mediators), including IL-5, Il- $1\beta$ , IL-17, and TNF- $\alpha$ , to a statistically significant extent, while up-regulating the primary anti-inflammatory cytokine, IL-10, measured two hours after endotoxin exposure.

Figure 3: NS2 Preclinical Anti-Inflammatory Efficacy Data

Source: Aldeyra Therapeutics, Inc.

The figure below shows the potential future target indications that Aldeyra intends to pursue with NS2, with the strategic focus primarily on dermatological and ophthalmic indications. In our view, this is a sound approach because these areas typically involve rapid, low-cost clinical development using objective, easily evaluable outcome measures; represent significant unmet medical needs; and do not require systemic exposure to drugs as they involve surface organs (the skin and the eyes).

Sjögren-Acute Ocular Discoid Larsson Anterior Lupus Rosacea(1) Syndrome **Uveitis** Rare Disease Rare Disease Rare Disease No FDA-Market with No FDA with Need for with Need for ffective Therapy without Toxicity Opportunity Approved ffective Therapy Therapy Therapy ithout Toxicity Topical Topical Formulation Topical Eye Drop Topical Eye Drop Dermatologic and Oral Issued Issued Issued Patents Matter Matter Matter Matter Phase I Phase III DATA EXPECTED IN SECOND HALF OF 2015: Phase II Sjögren-Larsson Syndrome (Dermatologic) Sjögren-Larsson Syndrome (Oral) Discoid Lupus Acute Anterior Uveitis Ocular Rosacea (1)

**Figure 4: Aldeyra Target Indications** 

Source: Aldeyra Therapeutics, Inc.

Aldeyra has also demonstrated the positive impact of NS2 on conditions such as scarring and mucositis, indicating that the drug could create a more permissive environment for tissue healing as well as suppress pro-inflammatory processes. As shown in the figure below, NS2 has shown positive effects when dosed chronically in a hamster model of oral mucositis – a condition that occurs relatively frequently in human subjects who are exposed to radiation therapy in order to ablate tumors. Aldeyra's lead molecule accelerated healing and decreased the frequency of ulceration in this model. We note that this preclinical evidence was generated using subcutaneous administration, showing that the drug is effective when dosed via different routes.

Hamster cheek pouch irradiation with 40 Gy (12.5mg/kg SQ BID NS2) 50% of Ulceration p<0.001 40% 30% 20% Days NS2 10% 0% Vehicle NS2 Day 36 p = 0.0110 12 14 16 18 22 24 26 30 % Animals with Ulceration Day 36 p<0.01 Day 28 Day 30 Day 34 Day 24 Day 26 Day 32 Day 36 Vehicle 90% 80% 50% 50% 20% 30% 40% NS2 50% 40% 20% 20% 20% 0% 0%

Figure 5: NS2 Healing Enhancement - Oral Mucositis Model

Source: Aldeyra Therapeutics, Inc.

The same model system revealed that NS2 had the ability to reduce radiation-induced scarring, as shown in the figure below. In our view, this may be evidence that the drug – in addition to having potent anti-inflammatory effects – can be deployed as an accelerator of tissue repair and potentially also as an anti-fibrotic in diseases such as cicatricial pemphigoid and morphea scleroderma.

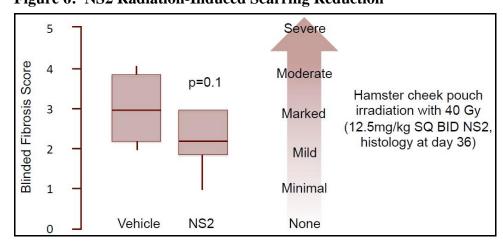


Figure 6: NS2 Radiation-Induced Scarring Reduction

Source: Aldeyra Therapeutics, Inc.

Given these results, we would note that Aldeyra may have a broad range of choices with respect to future clinical development of NS2 and other free aldehyde traps. These candidates may have applicability in both prescription as well as mass market consumer settings, and therefore could target highly substantive commercial opportunities. We are also encouraged by the fact that NS2 appears to be active in various formulations.

# **NS2 Clinical Development Plan**

The envisaged trial assessing NS2 safety and efficacy in SLS patients is extremely simple in nature, and consists of a 1:1 randomization design within a single-center, double-blinded, placebo-controlled format. Since SLS is such a rare disease, Aldeyra proposes to recruit 12 patients into this Phase 2 / 3 trial, with an evaluation period of eight weeks. We believe that the company should receive formal feedback from the FDA regarding this proposed plan within the coming months and thereafter is likely to file an Investigational New Drug (IND) application based on the final protocol. Assuming IND approval by the FDA and Institutional Review Board (IRB) approval at the site selected to conduct the trial, we expect enrollment in this study to begin late in 2014. Aldeyra is also working to finalize the cream-based formulation of NS2 that will be used in this trial.

Aldeyra is also slated to conduct a Phase 2 study in acute anterior uveitis, which is likely to follow a 1:1:1 randomization design and enroll approximately 45 patients in a double-blinded, comparator-controlled, multi-center setting. We anticipate that the three arms of the trial would involve NS2 alone, NS2 plus a sub-therapeutic dose of prednisolone acetate (a steroid often used in treatment of uveitis), and steroid alone, administered at the typical therapeutic dose (1% drops). We expect this trial to begin late in 2014 and yield data in the second half of 2015. The primary endpoint is likely to be cell count in the anterior chamber of the eye, a standardized readout in uveitis studies.

The figure below depicts the timeline for Aldeyra's clinical trials, which in addition to the Phase 2 / 3 trial in SLS and the Phase 2 trial in uveitis are likely to include a Phase 1 trial of the oral formulation of NS2 in SLS patients and two more Phase 2 studies in discoid lupus and ocular cicatricial pemphigoid. While these trials may not start in 2014, we believe that it is Aldeyra's intention to conduct them while the Phase 2 / 3 SLS study and Phase 2 uveitis study are running. The costs of these studies are relatively low, with Aldeyra's projections ascribing \$2 million – \$3 million in clinical development costs per trial. This is primarily due to the low numbers of patients that are planned to be enrolled.

2014 2015 2016 Sjögren-Larsson Sjögren-Larsson Syndrome Syndrome Phase II/III Phase III **NS2** Topical Dermatologic Discoid Lupus/Morphea Scleroderma Phase IIa Sjögren-Larsson Syndrome PO NS2 Oral Phase I Recurring Acute Anterior Uveitis Phase II NS<sub>2</sub> Topical Ocular Cicatricial Pemphigoid Eye Drop Phase II

Figure 7: Aldeyra Therapeutics Key Milestones Timeline

Source: Aldevra Therapeutics, Inc.

In our view, the Aldeyra clinical plan is rational and pragmatic, aimed at achieving the dual goals of navigating a rapid path to approval and market entry while also demonstrating activity across multiple disease areas and target organs with different drug formulations. This should, if successful, pave the way in the future for Aldeyra and / or its partners to pursue broader disease indications with NS2, such as eczema and fibrosis.

# **Commercial Perspectives**

In our view, NS2 could potentially become a roughly \$2 billion-a-year franchise at peak, simply by considering its potential in orphan dermatological and ophthalmic disorders. Given the small size of the sales force needed to commercialize the drug and favorable production costs, since this is an organic small molecule with a relatively simple chemical structure and cost-effective synthesis route, we expect high net profit margins.

Makers of orphan drugs have historically faced few obstacles to reimbursement from private or public insurers, despite prices that can amount to hundreds of thousands of dollars annually. However, payer sensitivity appears to be rising, as the launch rate of orphan drugs accelerates amid increasing pressure to contain costs. Patient access to orphan drugs is typically rarely denied, as the diseases that these drugs treat are typically severe, chronic unmet medical needs. However, to varying degrees, major U.S. reimbursement agencies are starting to use the full range of existing tools to ensure appropriate use of orphan agents. Simultaneously, trends in health plan design have increased the burden on patients through cost-sharing. Thus, even when access to orphan drugs is offered, providers and patients face hurdles that can affect utilization. Many payers expect orphan drug use management to intensify via the following trends:

- Scrutiny of orphan drug utilization beyond the \$50,000 per-patient annual threshold
- Focus on appropriate orphan drug use, often with restriction to approved indications
- Rising burden on patients through cost-sharing (i.e., coinsurance, higher copayments), as well as existing annual or lifetime maximum payments

#### **NS2 Market Model**

Since this is an orphan drug, we have assumed pricing at \$125,000 per patient annually in the U.S., which we consider achievable given the pricing of other drugs in ultra-orphan disorders such as Soliris (eculizumab) for treatment of paroxysmal nocturnal hemoglobulinuria (PNH), which is currently priced in excess of \$500,000 per patient annually. We note that NS2 drug pricing must be moderated in light of the fact that it is a small molecule drug and not a biologic. Ex-U.S., we anticipate that dermatology pricing should be in the \$100,000 range. For the ophthalmic market, we have assumed pricing in the U.S. at \$25,000 annually and in Europe at \$15,000 annually, reflecting the comparatively lower amounts of drug delivered via the eye drop formulation. Higher pricing may be achievable, based on Aldeyra's citation of the annual cost of a topical orphan drug (Targretin) to treat cutaneous lymphoma; this agent is priced at \$29/g, with dosing typically administered at 26g/m² twice-daily, treating 25% of the body surface. This corresponds to annual pricing at \$235,250 – while we do not assume that Aldeyra would be able to attain such pricing with NS2, it is of note that such benchmarks exist.

Our risk-adjusted Net Present Value (rNPV) assumptions are driven by the following key assumptions: a) we project that Aldeyra could market NS2 for orphan disorders independently in the U.S. and out-license the marketing rights for Europe and other ex-U.S. markets; b) we utilize a 15% discount rate applied to all future cash flows; c) we employ a 25% manufacturing and marketing offset to all revenues; d) we assume a royalty rate on ex-U.S. net sales of 10% – 18%, which we expect is likely to be conservative given the point at which Aldeyra might consider out-licensing the drug; e) we have utilized a 40% effective tax rate, under the assumption that Aldeyra is not likely to have significant net operating loss carry-forwards available to offset future taxable income. We regard these parameters as relatively conservative. Our model does not take into account the payment of milestones by Aldeyra's future partners, nor does it give Aldeyra credit at this juncture for the potential line extensions of NS2 into non-orphan indications, which could represent even more lucrative markets.

Table 3: NS2 Global Estimated Sales – Orphan Dermatological / Ophthalmic Disorders Market Size Model

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
United States																	
Sjögren-Larsson Syndrome (SLS) patients	1,200	1,224	1,248	1,273	1,299	1,325	1,351	1,378	1,406	1,434	1,463	1,492	1,522	1,552	1,583	1,615	1,647
Discoid lupus / morphea scleroderma patients	23,000	23,460	23,929	24,408	24,896	25,394	25,902	26,420	26,948	27,487	28,037	28,598	29,170	29,753	30,348	30,955	31,574
Acute anterior uveitis patients	36,000	36,720	37,454	38,203	38,968	39,747	40,542	41,353	42,180	43,023	43,884	44,761	45,657	46,570	47,501	48,451	49,420
Ocular cicatricial pemphigoid patients	38,000	38,760	39,535	40,326	41,132	41,955	42,794	43,650	44,523	45,414	46,322	47,248	48,193	49,157	50,140	51,143	52,166
Population Growth rate	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%
NS2 topical cream penetration	0.0%	0.0%	0.0%	0.1%	1.2%	3.4%	6.4%	8.5%	9.8%	12.0%	15.1%	19.1%	13.0%	6.7%	4.3%	2.2%	1.0%
NS2 topical eye drop penetration	0.0%	0.0%	0.0%	0.0%	0.5%	2.0%	3.7%	5.5%	7.5%	8.9%	10.4%	12.9%	11.4%	7.4%	4.9%	3.0%	1.4%
Patients receiving NS2 (cream)				25	314	908	1,757	2,375	2,791	3,482	4,452	5,759	4,003	2,111	1,388	732	349
Patients receiving NS2 (eye drop)					390	1,612	3,097	4,641	6,468	7,912	9,411	11,887	10,729	7,115	4,829	2,961	1,406
Cost of NS2 cream therapy (annual)				\$125,000	\$128,750	\$132,613	\$136,591	\$140,689	\$144,909	\$149,257	\$153,734	\$158,346	\$163,097	\$167,990	\$173,029	\$178,220	\$183,567
Cost of NS2 eye drop therapy (annual)					\$25,000	\$25,750	\$26,523	\$27,318	\$28,138	\$28,982	\$29,851	\$30,747	\$31,669	\$32,619	\$33,598	\$34,606	\$35,644
NS2 cream sales (\$ MM)	\$0.0	\$0.0	\$0.0	\$3.2	\$40.4	\$120.4	\$240.0	\$334.2	\$404.4	\$519.8	\$684.4	\$912.0	\$652.8	\$354.7	\$240.2	\$130.5	\$64.0
NS2 eye drop sales (\$ MM)	\$0.0	\$0.0	\$0.0	\$0.0	\$9.7	\$41.5	\$82.1	\$126.8	\$182.0	\$229.3	\$280.9	\$365.5	\$339.8	\$232.1	\$162.3	\$102.5	\$50.1
ROW (mainly Europe) markets																	
Sjögren-Larsson Syndrome (SLS) patients	1,500	1,530	1,561	1,592	1,624	1,656	1,689	1,723	1,757	1,793	1,828	1,865	1,902	1,940	1,979	2,019	2,059
Discoid lupus / morphea scleroderma patients	25,000	25,500	26,010	26,530	27,061	27,602	28,154	28,717	29,291	29,877	30,475	31,084	31,706	32,340	32,987	33,647	34,320
Acute anterior uveitis patients	33,000	33,660	34,333	35,020	35,720	36,435	37,163	37,907	38,665	39,438	40,227	41,031	41,852	42,689	43,543	44,414	45,302
Ocular cicatricial pemphigoid patients	40,000	40,800	41,616	42,448	43,297	44,163	45,046	45,947	46,866	47,804	48,760	49,735	50,730	51,744	52,779	53,835	54,911
Population Growth rate	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%
NS2 topical cream penetration	0.0%	0.0%	0.0%	0.0%	0.1%	1.1%	2.2%	3.9%	7.6%	10.6%	12.7%	13.8%	9.8%	5.5%	3.3%	2.2%	1.1%
NS2 topical eye drop penetration	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.6%	1.1%	2.4%	3.4%	4.9%	6.4%	4.4%	1.3%	0.4%	0.2%	0.1%
Patients receiving NS2 (cream)					16	326	664	1,195	2,349	3,364	4,114	4,563	3,291	1,869	1,168	774	405
Patients receiving NS2 (eye drop)						109	462	912	2,095	2,970	4,364	5,769	4,033	1,268	420	187	118
Cost of NS2 cream therapy (annual)					\$100,000	\$103,000	\$106,090	\$109,273	\$112,551	\$115,927	\$119,405	\$122,987	\$126,677	\$130,477	\$134,392	\$138,423	\$142,576
Cost of NS2 eye drop therapy (annual)					ψ.00,000	\$15,000	\$15,450	\$15,914	\$16,391	\$16,883	\$17,389	\$17,911	\$18,448	\$19,002	\$19,572	\$20,159	\$20,764
NS2 cream sales (\$ MM)	\$0.0	\$0.0	\$0.0	\$0.0	\$1.6	\$33.5	\$70.5	\$130.5	\$264.4	\$390.0	\$491.2	\$561.2	\$416.9	\$243.9	\$156.9	\$107.1	\$57.7
NS2 eye drop sales (\$ MM)	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$1.6	\$7.1	\$14.5	\$34.3	\$50.1	\$75.9	\$103.3	\$74.4	\$24.1	\$8.2	\$3.8	\$2.5
Global NS2 sales	\$0.0	\$0.0	\$0	\$3	\$52	\$197	\$400	\$606	\$885	\$1,189	\$1,532	\$1,942	\$1,484	\$855	\$568	\$344	\$174
Royalty rate on ex-U.S. NS2 sales	0%	0%	0%	0%	10%	10%	12%	15%	16%	17%	18%	18%	18%	18%	18%	18%	18%
Global revenue to Aldeyra Therapeutics	\$0.0	\$0.0	\$0.0	\$3.2	\$50.3	\$165.4	\$331.4	\$482.7	\$634.2	\$823.9	\$1,067.4	\$1,397.1	\$1,081.0	\$635.0	\$432.2	\$252.9	\$124.9

# **Ultra-Orphan Drug Pricing**

We believe that it is worthwhile to examine the current status of pricing for some of the world's most expensive drugs, which are deployed against ultra-rare diseases. Such factors provide some context regarding the potential future pricing for Aldeyra's therapeutics, particularly NS2 in Sjögren-Larsson Syndrome (SLS), which is an example of an ultra-rare disease with no currently-approved therapy.

The Orphan Drug Act of 1983 granted developers of drugs for diseases afflicting fewer than 200,000 people in the U.S. special tax considerations and an extra seven years of protection from competition, making these rare diseases a feasible market opportunity. Some 400 orphan drugs have been approved by the FDA since 1983, compared with only 38 prior to the passing of the Orphan Drug Act. In Europe, a rare disease is classified as a condition that afflicts no more than five cases per 10,000 individuals. According to the World Health Organization, a rare disease is a condition afflicting no more than 65 subjects per 100,000 individuals. The National Institute for Health and Care Excellence (NICE), an influential body driving drug pricing trends in the U.K., has defined ultra-rare diseases as conditions affecting no more than one subject per every 50,000 individuals. A market analysis issued by Thomson Reuters in August 2012, "The Economic Power of Orphan Drugs," found that many orphan drugs are as economically viable as medicines for far more common diseases. According to Thomson Reuters, ~25 million people in the U.S. alone suffer from rare diseases, and the worldwide value of the orphan drug market will be ~\$53 billion in 2014, about 7% of total pharmaceutical sales. The National Organization for Rare Disorders (NORD) has stipulated that there are over 7,000 known orphan diseases, with more discovered every year, but only about 200 have FDAapproved treatments. In our view, given the magnitude of this unmet need, the search for ultra-orphan disease treatments is certain to continue to drive the biotech industry.

Evidence seems to indicate that ultra-orphan drugs are priced according to rarity and what the manufacturer believes the market will bear; furthermore, close correlation exists between the price of an ultra-orphan drug and the numbers of available alternatives<sup>1</sup>. Genzyme (now Sanofi S.A.) was the first to charge a high price for imiglucerase, and other ultra-orphan drug products soon followed. Imiglucerase, an enzyme replacement therapy (ERT) for the treatment of Gaucher's disease, costs \$100,000 – \$400,000 per patient per year. Although there are only 2,000 patients in the United States and an estimated 6,000 patients worldwide, the revenue from imiglucerase approached \$1.8 billion in 2009. The drug still generates roughly \$1 billion annually in sales. Similarly, agalsidase beta (for Fabry's disease) and laronidase (for mucopolysaccharidosis type I), respectively cost an estimated \$200,000 and \$350,000 per year per patient.

In a study by Orofino, the average mean cost per patient across several European countries ranged from €3523 to €337,501 for 14 ultra-orphan medicinal products. The yearly cost of eculizumab (for paroxysmal nocturnal hemoglobinuria) is the highest, at over \$500,000 per patient. In 2013, eculizumab generated \$1.5 billion in sales. Remarkably, eculizumab was originally aimed at arthritis, and would probably have been priced in the range of similar products at \$20,000 per patient annually. Extraordinary price increases (>100% at a time) have been seen when established off-label use of a medicinal product in an ultra-rare condition became approved. For example, un-licensed use of 3,4-diaminopyridine for Lambert-Eaton myasthenic syndrome (LEMS) cost ~€1,000 per patient per year. The price of the marketed version is 50–70 times higher. In our view, NS2 can be classified as a form of "enzyme replacement therapy" (ERT), since it is designed to serve a function analogous to fatty aldehyde dehydrogenase, the enzyme that is defective in SLS patients. Therefore, this agent could potentially achieve pricing analogous to that seen for other ERTs in the ultra-orphan setting.

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<sup>&</sup>lt;sup>1</sup> Picavet et al., Orphan Drugs: Research and Reviews 3: 23-31 (2013)

Table 4: Ultra-Orphan Drug Pricing

Trade Name	Generic Name	Developer/Sponsor	Mechanism of Action	Disease Indication	Prevalence	Annual Cost	2013 sales	U.S. approval date
Soliris	eculizumab	Alexion Pharmaceuticals	Immunomodulation	Paroxysmal nocturnal hemoglobinuria (PNH)	1 in 77,000	\$409,000	\$1.5B	03/16/07
Naglazyme	galsulfase	BioMarin Pharmaceuticals	Enzyme replacement	Mucopolysaccharidosis type VI (MPS-VI)	1 in 215,000	\$390,000	\$271MM	05/31/05
Elaprase	idursulfase	Shire Pharmaceuticals / Genzyme (now Sanofi S.A.)	Enzyme replacement	Mucopolysaccharidosis type II (MPS-II) or Hunter syndrome	1 in 150,000	\$375,000	\$546MM	07/24/06
Cinryze	C1 esterase inhibitor	Shire plc (formerly ViroPharma) / Lev Pharmaceuticals	Enzyme inhibitor replacement	Hereditary angioedema (HAE)	1 in 50,000	\$350,000	\$400MM	10/13/08
Myozyme	interferon beta-1b	Genzyme (now Sanofi S.A.)	Enzyme replacement	Pompe's disease	1 in 40,000	\$300,000	\$680MM	04/28/06
Aldurazyme	laronidase	BioMarin Pharmaceutical	Enzyme replacement	Gaucher's disease	1 in 115,000	\$235,000	\$83.6MM	04/30/03
Cerezyme	imiglucerase	Genzyme (now Sanofi S.A.)	Enzyme replacement	Types I, II, and III Gaucher's disease	1 in 100,000	\$200,000	\$936MM	05/23/94
Fabrazyme	ceramide trihexosidase / alpha-galactosidase A	Genzyme (now Sanofi S.A.)	Reduction of globotriaosylceramide deposition in kidney capillary endothelium	Fabry's disease	1 in 40,000	\$200,000	\$520MM	04/24/03
Replagal	agalsidase alfa	Shire plc (originally Transkaryotic Therapies)	Reduction of globotriaosylceramide deposition in kidney capillary endothelium	Fabry's disease	1 in 40,000	\$200,000	\$468MM	EU-only; 2001

Source: National Institute for Health and Care Excellence (NICCE; UnitedHealth; U.S. Food and Drug Administration (FDA); EvaluatePharma

# **Aldehyde Trapping Overview**

The principle underlying Aldeyra's unique therapeutic approach and proprietary technology platform builds upon years of research characterizing the role of free aldehydes in the human body. Lipid peroxidation-derived aldehydes (LDAs) have been implicated in a number of oxidative stress-induced inflammatory pathologies such as diabetes, metabolic syndrome, vascular and neural degeneration, liver and kidney toxicity, cancer, retinopathy of prematurity, aging, and ischemia. One of the canonical pathways via which LDAs act is the signaling cascade mediated by the protein complex known as nuclear factor kappa-light-chain enhancer of activated B cells (NF $\kappa$ B).

The NF $\kappa$ B pathway is considered a central mediator of inflammatory processes in the human body, and regulates the downstream signaling of various pro-inflammatory cytokines, particularly tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1-beta (IL-1 $\beta$ ), and others<sup>2</sup>. The figure below depicts how the cascade induced by TNF- $\alpha$  is mediated through the NF $\kappa$ B protein complex, activated by I $\kappa$ B kinases, and results in the production of cytokines, chemokines, and various other inflammation-related molecules.

TNF-ox proteasome IKB kinases IKB-O IKB-a p50( p65 p65 nucleus p50( p65 mRNA IKB-0 IKB-CO citosol Cytokines Receptors Rel/NF-kB family IL1, IL2, IL2R, IL6 TLR2, TLR4, TLR9, hdb-c, p105, p100, CD40, GPR89 RelB Apoptose Growth Chemokines Adhesion regulators MCP-1, IL8, RANTES factors molecules Fas, BCL-2, c-Flip. G-CSE-GM-CSE ICAM-1, VCAM-1. caspases ECAM-1. P-selectin

Figure 8: Pro-inflammatory Cytokine NFκB Induction Signaling

Source: Redox Biology Group, University of Lisbon, Portugal

LDAs such as malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), and acrolein are generated upon degradation of lipid peroxides subsequent to free radical-induced peroxidation of membrane lipids, particularly the polyunsaturated fatty acids, in the biological membranes<sup>3</sup>. Arachidonic acid present in the biological membranes is predominantly susceptible to free radical attacks due to the presence of unsaturated bonds and is the primary source of LDAs, which are relatively more stable relative to free radicals such as oxygen and hydroxyl free radicals and act as highly reactive electrophilic molecules. Quantitatively, while HNE and MDA are the most abundant aldehydes formed subsequent to lipid peroxidation, acrolein is the most reactive one. However,

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<sup>&</sup>lt;sup>2</sup> Chandel *et al.*, Journal of Immunology 165: 1013-1021 (2000)

<sup>&</sup>lt;sup>3</sup> Loidl-Stahlhofen *et al.*, Biochimica et Biophysica Acta 1213: 1440-148 (1994)

LDAs in general have a tendency to react readily with the nucleophiles including thiols and amines containing cellular macromolecules such as proteins, and nucleic acids leading to cellular damage and accumulation of chemically altered macromolecules.

In various disease states, conjugates of LDAs with proteins and nucleic acids have been identified; for example, HNE-protein adducts were detected in mitotic, necrotic, and apoptotic cells in brain tumor tissues. LDAs can act as toxic secondary messengers to propagate redox signals, leading to cellular and tissue injury. The figure below depicts the manner in which lipid aldehyde-mediated inflammatory signaling is driven through the NFkB pathway, resulting in tissue damage and pathogenesis<sup>4</sup>. Since these lipid-derived free aldehydes are so long-lived and toxic, it is now thought that standard antioxidants are unlikely to have a significant therapeutic effect and more targeted approaches are required. Aldeyra, in our view, is in the vanguard of those developing therapeutic agents that specifically target these free aldehyde species.

External stimuli, infections, oxidants, cytokines Cell membrane NADPH oxidase Mitochondria Lipid alcohols Lipid-derived aldehydes (HNE) Polyol pathway GSSG Glucose GS-HNE NADPH NADPH . Aldose reductase ARI NADPH NADP NADP\* NADP Sorbitol GS-DHN Fructose Protein kinase signaling cascade NF-κB Gene transcription Cytokines, chemokines, growth Inflammation and factors, leukotrienes, other pathogenesis inflammatory mediators

Figure 9: Free Aldehyde Toxicity Cascade

Source: ADIS R&D Insights database

We note that the mechanism via which free aldehydes exert their pathogenic effects represents a canonical pro-inflammatory pathway. Accordingly, therefore, we consider the free aldehyde hypothesis highly plausible, and note that other firms have successfully pursued the development of drugs in the past that influence the NF $\kappa$ B pathway.

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<sup>&</sup>lt;sup>4</sup> Yadav and Ramana. Oxidative Medicine and Cellular Longevity 2013: 1-11 (2013)

# Background on Sjögren-Larsson Syndrome

Discovered in 1957, Sjögren-Larsson syndrome (SLS) is particularly common in certain Nordic geographies, particularly Sweden, where it was originally suggested by the disease's discoverers Torsten Sjögren and Tage Larsson that all the sufferers of the condition could trace their lineage back to a single common ancestor from 600 years ago. Currently, the prevalence of the disorder is very low, with only 1% of northern Sweden's population suffering from the disease. SLS is a rare autosomal, recessive, neurological and cutaneous disease<sup>5</sup>. This disease can be identified by a triad of medical disorders. The first is ichthyosis – a buildup of skin to form a scale-like covering that causes dryness and other problems (see figure below). The second identifier is spastic paraplegia, characterized by leg spasms. The final identifier is mental retardation. The SLS gene is found on chromosome 17. In order for a child to manifest SLS, both parents must be carriers of the SLS gene. If this is the case, their child has a 25% chance of getting the disease. No drugs are currently approved specifically to treat SLS.

Figure 10: Sjögren-Larsson Syndrome Disease Pathology



Source: Dermis.net

A point mutation (C943→T) has been discovered in seven of nineteen kindreds of European descent, accounting for 24% of the SLS alleles<sup>6</sup>. The C943T mutation was only found in patients of northern European ancestry from Sweden, the Netherlands, Germany, and Belgium. Haplotype analysis suggested that the patients carrying the C943T allele were distantly related. Since several Swedish patients studied were homozygous for C943T, this mutation has been hypothesized to be the major cause of SLS in the inbred Swedish families. The mutation leads to the substitution of serine for the highly conserved proline 315 in the fatty aldehyde dehydrogenase (FALDH) protein, and expression studies confirm that it destroys enzymatic activity.

The fatty aldehyde produced through catabolism of certain lipids is chiefly metabolized to fatty acid by FALDH (alternately known as ALDH3A2), which also functions to oxidize fatty alcohols as a component of the fatty alcohol: NAD oxidoreductase (FAO) enzyme complex. Genetic deficiency of FALDH/FAO in SLS patients results in accumulation of fatty aldehydes, fatty alcohols and related lipids (ether glycerolipids, wax esters) in cultured keratinocytes. These biochemical changes are associated with abnormalities in formation of lamellar bodies in the stratum granulosum and impaired delivery of their precursor membranes to the stratum corneum (SC). The defective extracellular SC membranes cause leakage in the epidermal water barrier and ichthyosis.

<sup>&</sup>lt;sup>5</sup> Rizzo, Molecular Genetics and Metabolism 65: 63-73 (1998)

<sup>&</sup>lt;sup>6</sup> De Laurenzi et al., Journal of Investigative Dermatology 109: 79-83 (1997)

# **Background on Acute Anterior Uveitis**

Uveitis – typically classified as a disorder of the ocular immune system – involves inflammation of the uvea, which consists of the middle, pigmented vascular structures of the eye and includes the iris, ciliary body, and choroid. These components are illustrated in the schematic of the human eye shown below. Acute anterior uveitis, which accounts for 70% - 90% of all cases, is limited only to the iris and anterior chamber of the eye.

Pupil Cornea Iris Posterior chamber Anterior chamber (aqueous humour) Zonular fibres Lens Ciliary muscle Suspensory ligament Retina Choroid Vitreous humour Sclera Hyaloid canal Optic disc Optic nerve Fovea Retinal blood vessels

Figure 11: Human Eye – Schematic Illustration

Source: Wikipedia

The disease manifests as ocular redness, irritation, and immune cell infiltration into the anterior chamber. Higher-potency corticosteroids (e.g., prednisolone acetate 1%) are generally employed to treat this condition. Lower-potency topical corticosteroids are often avoided initially because of limited concentrations achievable in the aqueous humor. Local injections, including intra-vitreal administration, are useful for episodic intermediate uveitis associated with decreased vision or with cystoid macular edema (CME). A short-term course of oral prednisone is sometimes needed, in addition to drops or injections for acute flares of uveitis. Chronic posterior or pan-uveitis requires longer oral therapy at a dose of 1mg/kg/day (60mg), followed by a slower taper to lower doses.

The main disadvantage of steroid usage in uveitis – despite the local administration typically utilized – is the incidence of significant side effects. Prednisone can cause bloating (the so-called "moon face" effect), water retention, high blood glucose, and changes in intra-ocular pressure (IOP), which can worsen vision. Therefore, we believe that there is a potential niche for a drug like NS2, which could reduce the inflammation without exposing patients to the unwanted side effects of steroid use.

# **Non-Orphan Indications Overview**

Free aldehyde trapping may have potential for the treatment of non-orphan indications. One of the most obvious line extension opportunities is in the area of skin diseases that manifest primarily via dryness, such as atopic dermatitis. The incidence of this condition, which is classified as a mucosal inflammatory disorder of unknown etiology, has been steadily rising in developed countries. It is estimated that 15% - 30% of children under the age of 18 and 2% - 10% of all adults suffer from this condition, which represents a tripling of the size of the affected population within just the past 30 years. The figure below shows the prevalence rates of eczema across different U.S. states.

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Figure 12: U.S. State Atopic Dermatitis Prevalence Rates

Source: Journal of Investigative Dermatology (2011)

Accordingly, therefore, we believe that this is a very attractive potential future market opportunity for Aldeyra, which the firm could pursue once NS2 has been proven to work in orphan indications. The figure below shows proof-of-concept efficacy data generated by Aldeyra with NS2, given intra-peritoneally, in two murine models of atopic dermatitis.

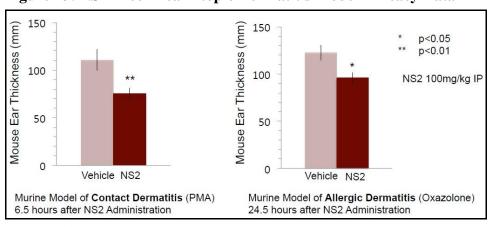


Figure 13: NS2 Preclinical Atopic Dermatitis Model Efficacy Data

Source: Aldeyra Therapeutics, Inc.

# **Intellectual Property Portfolio**

Aldeyra Therapeutics has systematically built an IP estate with the goal of providing tangible, long-term protection for its proprietary technology platform in the aldehyde trapping domain. Furthermore, the company possesses composition-of-matter protection on its lead drug candidate, NS2, along with method-of-use claims on the drug in the various disease indications wherein the firm plans to deploy it. We also note that, according to the Orphan Drug Act of 1983, compounds that receive Orphan Drug designation from the FDA are automatically entitled to seven years' market exclusivity post-launch in the United States.

**Table 5: Patent Estate** 

Patent Number	Title	Issue Date	Expiry Date	Country	Description
2006249866	Compositions and Methods for Treating Retinal Disease	1/25/12	5/26/2026	Australia	NS2-4 Composition of
ZI 200680026912.X	same	8/29/12	5/26/2026	China	same
1888548	same	8/22/13	5/26/2026	EPO	same
5042215	same	7/20/12	5/26/2026	Japan	same
289682	same	8/23/11	5/26/2026	Mexico	same
2419610	same	5/27/11	5/26/2026	Russia	same
7,973,025	same	7/5/11	8/15/2028	United States	same
2,609,659	same	1/28/2014	5/26/2026	Canada	same
1113797	same	8/23/2013	5/26/2026	Hong Kong	same
P0033274	same	3/22/2013	5/26/2026	Indonesia	same
1013425470000	same	12/11/2013	5/26/2026	South Korea	same

Source: Aldeyra Therapeutics, Inc.; U.S. Patent & Trademark Office

From our perspective, the patent estate protecting Aldeyra's marketed product portfolio represents a significant asset for a company of its size. The scientific and clinical acumen of the individuals who generated the data substantiating the claims in Aldeyra's IP portfolio is also a substantial risk-mitigating factor here, in our view. We believe the firm has successfully accomplished the task of assembling a relatively long-lived patent estate with which to protect its branded medicines from premature genericization.

Most important, however, we believe that Aldeyra's IP estate creates a moat around the firm's technology platform that represents a formidable barrier to competitors; indeed, we consider Aldeyra's IP so comprehensive that it is our assessment that any company seeking to develop a viable therapeutic approach involving free aldehyde trapping would likely need to seek a license from Aldeyra. As such, therefore, Aldeyra's IP portfolio does not merely protect the firm's own candidates, but could also prove to be a reliable source of licensing-based revenue in the future if the free aldehyde trapping hypothesis becomes the basis for significant future drug development activity.

Our assumptions are based on our view that Aldeyra has identified a specific type of organic small molecule that can be used to trap free aldehydes, and that competitors are likely to find it difficult to design small molecules with effective aldehyde-trapping properties that do not have similar structural features to Aldeyra's candidates. Accordingly, therefore, while Aldeyra cannot claim the principle of free aldehyde trapping itself, we believe the company is in a commanding position within this field and is thus likely to be able to leverage its IP portfolio strategically in the future.

## **Financial Review and Outlook**

**Revenue:** We do not forecast any revenue in 2014 and 2015, in accordance with Aldeyra Therapeutics' status as an emerging biopharmaceutical company with no commercial-stage products on the market. The firm does not provide financial guidance.

- ♦ NS2 Phase 2/3 Study Enrollment Initiation: We anticipate the initiation of enrollment in a Phase 2/3 trial of NS2 in patients with Sjögren-Larsson Syndrome (SLS) in the U.S. in late 2014.
- ◆ Top-Line Phase 2 / 3 Data: In our view, assuming timely enrollment completion in the Phase 2 / 3 trial of NS2 in the U.S., top-line data could become available early in the second half of 2015. We would anticipate that − if this data is positive − Aldeyra is likely to begin a confirmatory Phase 3 trial of NS2 in SLS in late 2015, with data potentially available in mid-2016. Regulatory submission could occur in late 2016. Assuming Priority Review for the drug, which could occur as a result of the fact that NS2 would be expected to have Orphan Drug status although it is not a given, approval could come in early 2017. However, we do not factor this into our assumptions.
- ♦ NS2 Proof-of-Concept Opthalmology Clinical Data: We anticipate that Aldeyra could begin the clinical development of a topical eye drop formulation of NS2 in acute anterior uveitis late in 2014 and unveil results from a proof-of-concept clinical trial in the second half of 2015.

**Gross Margins:** We project that the gross margins on Aldeyra's late-stage agents could reach 85% - 90%, in keeping with the margins typically seen on organic small molecule drugs in the pharmaceutical industry. We would also recommend that investors note the pricing environment for NS2 in SLS, which is likely to improve gross margins much further since the drug could be priced at up to \$125,000 per patient annually (or more, given the Targretin example). We would expect Aldeyra to establish a small proprietary sales force to commercialize the drug in the U.S. and partner with specialty distributors in ex-U.S. markets, chiefly Europe, in order to optimize the value of the drug.

**Operating Expenses:** For 2014 and 2015, we estimate operating expense levels that are significantly higher than those in 2011 and 2012. We estimate R&D expenses to rise significantly as Aldeyra ramps up clinical development.

**Taxes:** The tax benefit of losses in excess of the maximum amount that may be used in future years has been eliminated. We have modeled a 40% effective tax rate.

**Share Count:** The outstanding *pro forma* fully-diluted share count stands at roughly 6.9 million shares. The fully-diluted shares include 1.2 million outstanding options (approximately 470,000 options belonging to the option pool for future awards to employees) and 60,000 warrants issued to the firm's underwriter. Given the company's cash position, strategic goals, and capital structure, a share repurchase program is unlikely, in our view.

**EPS:** We forecast a net loss of \$1.47 per share in 2014, and \$1.78 per share in 2015.

**Balance Sheet:** The firm currently holds roughly \$12 million in cash and equivalents (*pro forma*), following its recent IPO. We anticipate that the current cash balance should be sufficient to fund operations into late 2015.

# **Management Team**

The firm seeks to align the management team's interests with those of shareholders by using equity-based incentive awards. Aldeyra's management team members have extensive experience in the pharmaceutical industry, particularly in drug development.

#### Todd C. Brady, M.D., Ph.D.

President & Chief Executive Officer

Dr. Brady has more than 18 years of pharmaceutical clinical and business development experience. Prior to joining Aldexa as President and CEO in 2011, Dr. Brady was an entrepreneur-in-residence and principal at Domain Associates, where he led institutional financing in numerous biotechnology companies from 2004 to 2013. Prior to joining Domain, Dr. Brady was a co-founder and CEO of Phenome Sciences, a biotechnology firm he merged with Xanthus Pharmaceuticals (subsequently acquired by Antisoma), where he was later executive vice president of Strategic Development and Planning. Dr. Brady also worked as head of business development and medical director at Aderis Pharmaceuticals (acquired by Schwarz Pharma, now part of UCB). While at Xanthus and Aderis, Dr. Brady was a medical consultant on numerous pre-clinical programs and clinical programs in Phases I through IV, including Neupro<sup>®</sup>, a drug now marketed for Parkinson's disease. Dr. Brady holds an M.D. from Duke University Medical School, a Ph.D. from Duke University Graduate School, and an A.B. from Dartmouth College.

#### Scott L. Young

Chief Operating Officer

Mr. Young has more than 25 years of pharmaceutical pre-clinical and clinical development experience. Prior to joining Aldexa Therapeutics in December 2011 as Chief Operating Officer (COO), he held the same position at Link Medicine, Inc., a biotechnology company developing novel pharmaceuticals to treat neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. While at Link Medicine, Mr. Young and colleagues successfully raised more than \$40 million in financing, advanced the lead program to clinical development, and subsequently out-licensed the technology to AstraZeneca. Mr. Young also served as COO for OXiGENE, Inc., a publicly-traded, NASDAQ-listed oncology therapeutics development company, where, during the eight years of his tenure, he was instrumental in advancing a pharmaceutical candidate from laboratory testing into Phase 3 clinical trials and led the development of a compound in an orphan ophthalmology indication. Mr. Young has also held positions in clinical and regulatory affairs, GMP manufacturing operations and R&D and process development at Genzyme Corporation, Repligen Corp. and Genetics Institute (now Pfizer). He holds a B.S. in biochemistry from the University of Massachusetts, Amherst.

# **Board of Directors**

#### C. Boyd Clarke

Chairman of the Board

Mr. Clarke's original training in the pharmaceutical and vaccine industry was received at Merck & Co., one of the world's largest pharmaceutical companies, where he held a number of positions, including Vice President of the Merck Vaccine Division and the founding President of Pasteur-Merieux Merck, Sharp & Dohme (MSD), a European joint venture that commercialized vaccines in the European Union. Since leaving Merck in 1996, his career has focused on leading and advising smaller developmental biotechnology and vaccine companies. Mr. Clarke was previously President and Chief Executive Officer of three biotechnology companies: Neose Technologies, a protein therapeutics company; Aviron, a vaccine company; and U.S. Bioscience, an oncology company. MedImmune acquired both Aviron and U.S. Bioscience (in 1999) for a combined value of \$2 billion. Mr. Clarke has served as Chairman of the Board of QLT

Therapeutics (an ocular disease-focused company) and Mersana Therapeutics (an oncology company), and as Executive Chairman of LigoCyte Pharmaceuticals (a vaccine company), in which he oversaw the sale of the company to Takeda Pharamceuticals in 2012. He has also served as a board member or advisor to OraVax (a vaccine company) and Rib-X Pharmaceuticals, now known as Melinta Therapeutics (an antibiotics developer). In these capacities, he has developed significant expertise in the challenges of emerging firm leadership, strategic management, business development, and M&A.

#### Todd C. Brady

Executive Director See bio above.

#### Martin J. Joyce, M.B.A.

Non-Executive Director

Mr. Joyce's professional background includes leadership roles in public and private, medical device, biotechnology and pharmaceutical companies from start-up stage to over \$500 million in annual revenue. He has experience in public equity financing, business development, SEC reporting, strategic planning, mergers, acquisitions, investor relations and biotechnology operations. Since 2012, Mr. Joyce has served as a consultant to the life science industry assisting biotechnology and pharmaceutical companies in strategic planning, fund raising and operations. Prior to joining Aldexa Therapeutics, Mr. Joyce was Chief Financial Officer at Lucid Inc., an early stage skin cancer diagnostic company; Executive Vice President and Chief Financial Officer of BioSphere Medical; and North American Chief Financial Officer for Serono Inc., a biotechnology company (now part of Merck KgaA). Mr. Joyce has also served as Managing Partner of Stratex Group, LLC, a provider of biopharmaceutical executive services to early stage companies and venture investors, and was previously employed at Millipore Corp., a high technology bioscience company. Mr. Joyce received a B.S. in finance from Northeastern University and a M.B.A. from Suffolk University, Boston, Massachusetts.

#### Gary Phillips, M.D., M.B.A.

Non-Executive Director

Dr. Phillips has served as Senior Vice President and Chief Strategy Officer at Mallinckrodt Pharmaceuticals since October 2013 and has been a member of the Aldeyra board since May 2009. Prior to joining Aldexa Therapeutics, Dr. Phillips was President of Reckitt Benckiser Pharmaceuticals, Inc., President of U.S. Surgical and Pharmaceuticals at Bausch & Lomb Inc., and has held executive roles at Merck Serono SA (a division of Merck KGaA), Novartis Corporation, and Wyeth Pharmaceuticals, Inc. (now Pfizer, Inc.). He was most recently Head of Global Health & Healthcare Industries at the World Economic Forum in Geneva from January 2012 to September 2013. Dr. Phillips was also healthcare strategy managing consultant at Towers Perrin Forster & Crosby, Inc (now Twoers Warson & Co.), and practiced as general medicine clinician/officer in the U.S. Navy, from which he was honorably discharged as a lieutenant commander. Dr. Phillips was educated at the University of Pennsylvania, where he received an M.D. degree (Alpha Omega Alpha) from the School of Medicine in 1992, an M.B.A. from the Wharton School in 1991, and B.A. (summa cum laude, Phi Beta Kappa) in biochemistry from the College of Arts and Sciences in 1987. He completed his post-graduate medical education at the Naval Medical Center in San Diego, CA, and maintains an active medical license.

#### Ben Bronstein, M.D., M.B.A.

Non-Executive Director

Dr. Bronstein has served as a member of the company's board of directors since 2010, and from 2010 to 2011 served as CEO of Aldexa Therapeutics, then known as Neuron Systems. Dr. Bronstein is a Visiting Scholar at the Wyss Institute of Biologically Inspired Engineering at Harvard Medical School and an active advisor to life science

companies. He is a board-certified pathologist and dermatopathologist, with more than 20 publications. Dr. Bronstein began his professional career on the staff of the Massachusetts General Hospital and on the faculty of Harvard Medical School. He has spent the past 25 years in entrepreneurial roles in life science companies and venture capital firms. Dr. Bronstein has founded or held senior management positions at several venture-backed life science firms, including BioSurface Technologies Corporation, a regenerative medicine company; Peptimmune, Inc., an immunotherapeutics company (a spin-out from Harvard and MIT); and Vidus Ocular, Inc., a Yale University spin-out developing an implantable device for the treatment of glaucoma. Most recently he has served as a founder and senior Vice President of Access BridgeGap Ventures, the life science investment unit of Access Industries, Inc. Dr. Bronstein serves on the board of directors of several privately held life science firms. He is also a member of the Weill Cornell Medical College Faculty Industry Council and the Coulter Oversight Committee at Boston University, and received his M.D. and M.B.A. from Boston University.

#### Neal Walker, D.O., M.B.A.

Non-Executive Director

Dr. Walker is the President and CEO at Aclaris Therapeutics, Inc., a privately held dermatological disorders-focused drug development company. He is a board-certified dermatologist and serial entrepreneur with over 18 years of experience in biopharmaceutical industry. Prior to founding Aclaris Therapeutics, Inc. in 2012, he was co-founder, President and CEO of Vicept Therapeutics, Inc. (acquired by Allergan, Inc.). Dr. Walker has co-founded a led a number of life science companies, including: Octagon Research Solutions, Inc., a software and services provider to biopharmaceutical companies (acquired by Accenture plc); Trigenesis Therapeutics, Inc., a specialty dermatology company where he served as Chief Medical Officer (acquired by Dr. Reddy's Laboratories Ltd.); and Cutix Inc., a commercial dermatology company that markets PreSun(R), a sunscreen brand acquired from Bristol-Myers Squibb Co. He began his pharmaceutical industry career at Johnson and Johnson. Dr. Walker currently is on the Board of Directors of Sebacia, Inc and Follica, Inc (Executive Chairman). He previously served on the Board of Directors for Octagon, a contract research organization, and is also on the Advisory Board of Flexible Medical Systems LLC, a privately held medical device company. Dr. Walker received his M.B.A. from The Wharton School, University of Pennsylvania, his D.O. from Philadelphia College of Osteopathic Medicine and a B.A. in Biology from Lehigh University.

#### Jesse I. Treu, Ph.D.

Non-Executive Director

Dr. Treu has been a Managing Member of Domain Associates, L.L.C. since its inception in 1986. He has been a director of over 35 early-stage healthcare companies. Dr. Treu currently serves as a member of the boards of directors of Afferent Pharmaceuticals, Inc., CoLucid Pharmaceuticals, Inc., Regado Biosciences, Inc., Tandem Diabetes Care, Inc., RightCare Solutions, Inc. and Veracyte, Inc. He has also served as a founder, president and chairman of numerous venture-stage companies. Prior to the formation of Domain Associates, Dr. Treu had twelve years of experience in the healthcare industry. He was Vice President of the predecessor organization to The Wilkerson Group and its venture capital arm, CW Ventures. While at CW Ventures, he served as President and CEO of Microsonics, Inc., a pioneer in computer image processing for cardiology. From 1977 through 1982, Dr. Treu led new product development and marketing planning for immunoassay and histopathology products at Technicon Corp., which is now part of Siemens Diagnostics. He began his career with General Electric Company in 1973, initially as a research scientist developing thin film optical sensors for immunoassay testing, and later serving on the corporate staff with responsibility for technology assessment and strategic planning. Dr. Treu received his B.S. in Physics from Rensselaer Polytechnic Institute and his M.A. and Ph.D. in physics from Princeton University.

Table 6: Aldeyra Therapeutics (ALDX) – Historical Income Statements, Financial Projections

FY end December 31

\$ in thousands, except per share data

				•	2014		•	2015E						
	2011A	2012A	2013A	1QA	2QE	3QE	4QE	2014E	1QE	2QE	3QE	4QE	2015E	
Revenue														
Product revenue	-	-	-	-	-	-	-	-	-	-	-	-	-	
Service revenue	-	-	-	-	-	-	-	-	-	-	-	-	-	
Research and other	-	-	-	-	-	-	-	-	-	-	-	-	-	
Total revenue	-	-	-	-	-	-	-	-	-	-	-	-	-	
Expenses														
Cost of product and service revenue	-	-	-	-	-	-	-	-	-	-	-	-	-	
Research & development	1,365	469	1,542	444	600	800	1,000	2,844	1,200	1,500	1,800	2,000	6,500	
Selling and marketing	-	-	-	-	-	-	-	-	-	-	-	-	-	
General and administrative	744	645	2,135	801	850	900	950	3,501	1,000	1,100	1,200	1,300	4,600	
Total expenses	2,109	1,114	3,676	1,245	1,450	1,700	1,950	6,345	2,200	2,600	3,000	3,300	11,100	
Gain (loss) from operations	(2,109)	(1,114)	(3,676)	(1,245)	(1,450)	(1,700)	(1,950)	(6,345)	(2,200)	(2,600)	(3,000)	(3,300)	(11,100)	
Other income/expense														
Interest income/expense	(275)	(342)	(159)	(113)	(100)	(90)	(80)	(383)	(150)	(140)	(120)	(110)	(520)	
Realized loss on marketable securities														
Other income/expense	(210)	(37,670)	4,946	1,345	-	-	-	1,345	-	-	-	-	-	
Total investment income and other	(485)	(38,012)	4,786	1,232	(100)	(90)	(80)	962	(150)	(140)	(120)	(110)	(520)	
Loss before provision for income taxes	(2,593)	(39,126)	1,110	(13)	(1,550)	(1,790)	(2,030)	(5,383)	(2,350)	(2,740)	(3,120)	(3,410)	(11,620)	
Deferred income tax benefit	-	-	-	-	-	-	-	-	-	-	-	-	-	
Net loss/income	(2,593)	(39,126)	1,110	(13)	(1,550)	(1,790)	(2,030)	(5,383)	(2,350)	(2,740)	(3,120)	(3,410)	(11,620)	
Net loss per share (basic)	(8.25)	(124.44)	3.49	(0.04)	(0.53)	(0.32)	(0.36)	(1.49)	(0.41)	(0.48)	(0.46)	(0.43)	(1.78)	
Net loss per share (diluted)	(8.25)	(124.44)	(17.58)	(0.04)	(0.53)	(0.32)	(0.36)	(1.47)	(0.41)	(0.48)	(0.46)	(0.43)	(1.78)	
Weighted average number of shares outstanding (basic)	314	314	318	327	2,940	5,590	5,640	3,625	5,690	5,740	6,790	7,840	6,515	
Weighted average number of shares outstanding (diluted)	314	314	857	444	2,940	5,590	5,640	3,654	5,690	5,740	6,790	7,840	6,515	

Table 7: Aldeyra Therapeutics (ALDX) – Historical Balance Sheet, Financial Projections

FY end December 31

\$ in thousands, except per share data

					2014	E				2015	E		
	12/31/11A	12/31/12A	12/31/13A	3/31A	6/30	9/30	12/31	12/31/14E	3/31	6/30	9/30	12/31	12/31/15E
Assets													
Current assets:													
Cash and cash equivalents	251	1,224	3,262	2,146	11,962	10,252	12,822	12,822	10,522	7,832	27,082	23,722	23,722
Marketable securities	-	-	-	-	-	-	-	-	-	-	-	-	-
Restricted cash	-	-	-	-	-	-	-	-	-	-	-	-	-
Accounts receivable	-	-	-	-	-	-	-	-	-	-	-	-	-
Inventories		-											
Other assets and prepaid expenses	4	753	481	10	10	10	10	10	10	10	10	10	10
Total current assets	255	1,977	3,743	2,155	11,971	10,261	12,831	12,831	10,531	7,841	27,091	23,731	23,731
Property and equipment	4	-	-	-	-	-	-	-	-	-	-	-	-
Intangible assets	-	-	-	-	-	-	-	-	-	-	-	-	-
Restricted cash	-	-	-	-	-	-	-	-	-	-	-	-	-
Marketable securities													
Other assets	-	-	-	735	735	735	735	735	735	735	735	735	735
Total Assets	259	1,977	3,743	2,891	12,707	10,997	13,567	13,567	11,267	8,577	27,827	24,467	24,467
Liabilities and shareholder equity													
Current liabilities													
Accounts payable	25	73	342	166	166	166	166	166	166	166	166	166	166
Accrued expenses	81	124	118	133	133	133	133	133	133	133	133	133	133
Accrued acquisition and integration costs	-	-	-	-	-	-	-	-	-	-	-	-	-
Deferred revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Current portion of long-term debt	-	-	-	-	-	-	-	-	-	-	-	-	-
Other current liabilities	2,487	167	145	392	392	392	392	392	392	392	392	392	392
Total current liabilities	2,593	363	605	692	692	692	692	692	692	692	692	692	692
Deferred revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Other long-term liabilities	-	26,768	5,042	3,336	3,336	3,336	3,336	3,336	3,336	3,336	3,336	3,336	3,336
Long-term accrued acquisition costs	-	-	-	-	-	-	-	-	-	-	-	-	-
Long-term deferred tax liability	-	-	-	-	-	-	-	-	-	-	-	-	-
Total Liabilities	2,593	27,132	5,647	4,027	4,027	4,027	4,027	4,027	4,027	4,027	4,027	4,027	4,027
Shareholder's equity													
Common stock	13,182	29,234	39,420	38,509	38,511	38,511	38,511	38,511	38,511	38,511	38,513	38,513	38,513
Additional paid-in capital	-	-	-	1,277	12,591	12,591	17,091	17,091	17,091	17,091	39,409	39,409	39,409
Accumulated other comprehensive income	-	-	-	-	-	-	-	-	-	-	-	-	-
Deficit accumulated	(15,517)	(54,388)	(41,324)	(40,923)	(42,423)	(44,133)	(46,063)	(46,063)	(48,363)	(51,053)	(54,123)	(57,483)	(57,483)
Total shareholder's equity	(2,335)	(25,155)	(1,904)	(1,137)	8,679	6,969	9,539	9,539	7,239	4,549	23,799	20,439	20,439
Total liability and shareholder's equity	259	1,977	3,743	2,891	12,707	10,997	13,567	13,567	11,267	8,577	27,827	24,467	24,467

Table 8: Aldeyra Therapeutics (ALDX) – Historical Statement of Cash Flows, Financial Projections

FY end December 31

\$ in thousands, except per share data

					2014	E				2015	E		
	2011A	2012A	2013A	1QA	2QE	3QE	4QE	2014E	1QE	2QE	3QE	4QE	2015E
Cash flows from operating activities													
Net loss	(2,378)	(23,075)	13,060	402	(1,550)	(1,790)	(2,030)	(4,968)	(2,350)	(2,740)	(3,120)	(3,410)	(11,620
Adjustments for:	, ,	, , ,	· ·		, ,	, ,	, ,	, ,	, ,	, ,	, ,	, ,	
Stock-based compensation	50	84	1,702	366	50	80	100	596	50	50	50	50	200
Depreciation & amortization	2	4	-	88	-	-	-	88	-	-	-	-	-
Other non-cash expense	-	22,117	(16,728)	(1,760)	-	-	-	(1,760)	-	-	-	-	-
Change in operating assets & liabilities													
Accounts receivable	-	-	-	-	-	-	-	-	-	-	-	-	-
Inventories	-	-	-	-	-	-	-	-	-	-	-	-	-
Other current assets	280	1	(5)	(1)	-	-	-	(1)	-	-	-	-	-
Accounts payable	(166)	47	269	(176)	-	-	-	(176)	-	-	-	-	-
Deferred revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Other liabilities	(181)	43	(4)	18	-	-	-	18	-	-	-	-	-
Total change in operating assets & liabilities	(66)	92	260	(159)	-	-	-	(159)	-	-	-	-	-
Cash flows from operating activities	(2,393)	(778)	(1,707)	(1,064)	(1,500)	(1,710)	(1,930)	(6,204)	(2,300)	(2,690)	(3,070)	(3,360)	(11,420
Cash flows from investing activities													
Investment in PPE	-	-	-	-	-	-	-	-	-	-	-	-	-
Maturity (purchase) of marketable securities	-	-	-	-	-	-	-	-	-	-	-	-	-
Cash flows from investing activities	-	-	-	-	-	-	-	-	-	-	-	-	-
Cash flows from financing activities													
Proceeds from long-term debt	-	500	1,170	-	-	-	4,500	4,500	-	-	-	-	-
Repayments on asset-backed loan	-	-	-	-	-	-	-	-	-	-	-	-	-
Repayment of long-term debt	-	-	(104)	-	-	-	-	-	-	-	-	-	-
Proceeds from issuance of common stock and warrants	-	1,251	2,679	(53)	11,316	-	-	11,263	-	-	22,320	-	22,320
Cash flows from financing activities	-	1,751	3,745	(53)	11,316	-	4,500	15,763	-	-	22,320	-	22,320
Net increase/ decrease in cash and cash equivalents	(2,393)	973	2,039	(1,117)	9,816	(1,710)	2,570	9,559	(2,300)	(2,690)	19,250	(3,360)	10,900
Effect of exchange rate	- '	-	-	-	· -	-	-	-	-	-	-	-	
Cash and cash equivalents, beginning of period	2,644	251	1,224	3,262	2,146	11,962	10,252	3,262	12,822	10,522	7,832	27,082	12,822
Cash and cash equivalents, end of period	251	1,224	3,262	2,146	11,962	10,252	12,822	12,822	10,522	7,832	27,082	23,722	23,722

## **Public companies mentioned in this report:**

Alexion Pharmaceuticals (ALXN/NASDAQ)

Auspex Pharmaceuticals (ASPX/NASDAQ)

BioMarin Pharmaceutical Co. (BMRN/NASDAQ)

Bluebird bio (BLUE/NASDAQ)

Catalyst Pharmaceutical Partners (CPRX/NASDAQ – Buy)

Evoke Pharma (EVOK/NASDAQ – Buy)

Galectin Therapeutics (GALT/NASDAQ – Buy)

Lpath (LPTN/NASDAQ)

Opexa Therapeutics (OPXA/NASDAQ - Buy)

Retrophin (RTRX/NASDAQ)

Sanofi S.A. (SNY/NYSE)

Shire plc (SHPG/NASDAQ)

StemCells (STEM/NASDAQ)

Stemline Therapeutics (STML/NASDAQ – Buy)

Synergy Pharmaceuticals (SGYP/NASDAQ - Buy)

Ultragenyx (RARE/NASDAQ)

## **Required Disclosures**

## **Price Target**

Our 18-month price target is \$35.00 per share.

## Valuation Methodology

Given the fact that Aldeyra is currently unprofitable, we use a discounted cash flow-based approach to value the shares. Based on a comparables analysis, we believe that the stock is worth \$35.00 per share, given our estimate of a \$300 million risk-adjusted net present value (rNPV) for the firm's pipeline. This assumes that the shares trade in line with the comp group average enterprise value of \$300 million and that the firm has roughly 9 million shares outstanding and ~\$26 million in cash at the end of 2015.

#### Risk Factors

Issues that could prevent the achievement of our price objective include, but are not limited to, clinical, regulatory, competitive, reimbursement and financial risks. Drugs in clinical development may not advance due to inadequate safety, efficacy, or tolerability. Regulatory agencies may decline to approve regulatory submissions in a timely manner, or may not approve a drug candidate at all. The firm may require substantial funding to complete the clinical development of its candidates and establish commercial infrastructure, which could be dilutive to current shareholders. We expect competition for the company's drugs from several public and private companies developing pharmaceuticals. Future sales of the firm's drugs could depend upon reimbursement from private, as well as public, reimbursement agencies.

## For important disclosures go to www.aegiscap.com.

Research analyst compensation is dependent, in part, upon investment banking revenues received by Aegis Capital Corp.

Aegis Capital Corp. intends to seek or expects to receive compensation for investment banking services from the subject company within the next three months.

Aegis Capital Corp. has performed investment banking services for and received fees from Stemline Therapeutics, Inc. within the past 18 months.

Aegis Capital Corp. has performed investment banking services for and received fees from Galectin Therapeutics, Inc. and Synergy Pharmaceuticals, Inc. within the past 24 months.

Aegis Capital Corp. has performed investment banking services for and received fees from Aldeyra Therapeutics Inc., Evoke Pharma, Inc. and Opexa Therapeutics. Inc. within the past 12 months.

Aegis Capital Corp. makes a market in Aldeyra Therapeutics Inc., Evoke Pharma, Inc. and Stemline Therapeutics, Inc.,

## Investment Banking Services/Past 12 Mos.

Rating	Percent	Percent
BUY [BUY]	83.02	50.00
HOLD [HOLD]	16.98	22.22
SELL [SELL]	0.00	0.00

#### Meaning of Ratings

- A) A Buy rating is assigned when we do not believe the stock price adequately reflects a company's prospects over 12-18 months.
- B) A Hold rating is assigned when we believe the stock price adequately reflects a company's prospects over 12-18 months.

C) A Sell rating is assigned when we believe the stock price more than adequately reflects a company's prospects over 12-18 months.

#### **Other Disclosures**

The information contained herein is based upon sources believed to be reliable but is not guaranteed by us and is not considered to be all inclusive. It is not to be construed as an offer or the solicitation of an offer to sell or buy the securities mentioned herein. Aegis Capital Corp., its affiliates, shareholders, officers, staff, and/or members of their families, may have a position in the securities mentioned herein, and, before or after your receipt of this report, may make or recommend purchases and/or sales for their own accounts or for the accounts of other customers of the Firm from time to time in the open market or otherwise. Opinions expressed are our present opinions only and are subject to change without notice. Aegis Capital is under no obligation to provide updates to the opinions or information provided herein. Additional information is available upon request.

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