June 2, 2014

WELLS FARGO SECURITIES

Equity Research

Alder Biopharmaceuticals, Inc.

ALDR: We Initiated Coverage With An Outperform Rating

Outperform / V

Sector: Biotechnology
Market Weight

Initiation of Coverage

- **Summary:** We have initiated coverage of ALDR with an Outperform rating and a $22-24 valuation range. We believe the company's two lead assets, ALD403 for migraine and Clazakizumab for autoimmune diseases, both have strong efficacy/safety profiles, clear paths to approval, and blockbuster potential. We believe ALDR shares considerably undervalue the future milestone, royalty, and sales revenue the two agents could generate and expect appreciation for the stock as the programs progress. Our valuation is based on a blend of probability-adjusted, discounted out-year EPS and revenue multiples.
- **We believe ALD403 puts ALDR on the leading edge of a potential significant shift in migraine treatment, providing a future blockbuster opportunity.** ALD403 is part of an emerging class, anti-CGRP antibodies, being developed specifically for the reduction in migraines attacks for frequent headache sufferers. In a recently reported proof-of-concept study, a single IV dose of '403 significantly reduced headache frequency for months, with some patients becoming headache-free, with no safety signals. Though additional studies will need to be done to optimize dose and delivery and confirm long-term benefits, barring emergence of any toxicity we believe the agent has a good probability of ultimately gaining approval -- particularly given that it already demonstrated benefits on a registration-enabling endpoint. Our physician feedback suggests a drug of this profile would be embraced by clinicians and patients, alike, and even allowing for other competing anti-CGRP entrants, we believe the market is large enough such a $1.5B+ market opportunity could be readily achievable.
- **We believe Clazakizumab could be a competitive entrant in the large RA/PsA space that can generate meaningful milestone and royalty revenue for ALDR.** Clazakizumab, an anti-IL-6 antibody completing phase II for RA, has demonstrated efficacy and safety comparable to other biologics for the disease in several studies and has a validated mechanism, making it highly likely to ultimately reach the market, in our view. Though the autoimmune development and commercial space is highly crowded, we believe Clazakizumab has several features that could provide it with an advantageous overall profile among non-TNF therapies, and we believe even a relatively small slice of the large RA/PsA market and use primarily after anti-TNFs would still generate $1.5B+ in sales and $250MM+ in royalties to ALDR -- helped by the commercial experience of its partner, BMY. Additionally, the pre-commercial milestones receivable from partner BMY in RA, which we believe are low risk, should generate nearly $400MM for ALDR in the coming years -- themselves even more than the company's current market cap.

Valuation Range: $22.00 to $24.00
Our valuation range is based on applying a 30x multiple to our 2020 estimated EPS and discounting at 15%, blended with 3x sales multiple of 2020 estimated sales, and discounting at 12%. Risks include emergence of a safety signal, and competition in the migraine/RA spaces.

Investment Thesis:
We believe Alder is undervalued based on the long-term promise of ALD403 and Clazakizumab.

EPS	2013A	2014E Curr.	2014E Prior	2015E Curr.	2015E Prior
Q1 (Mar.)	NE	($0.25)	NC	NE	NC
Q2 (June)	NE	(0.26)	NC	NE	NC
Q3 (Sep.)	NE	(0.24)	NC	NE	NC
Q4 (Dec.)	NE	(0.25)	NC	NE	NC
FY	($0.94)	($1.00)	NC	($0.15)	NC
CY	($0.94)	($1.00)		($0.15)	
FY P/E	NM	NM		NM	
Rev.(MM)	$19	$17		$51	

Source: Company Data, Wells Fargo Securities, LLC estimates, and Reuters
NA = Not Available, NC = No Change, NE = No Estimate, NM = Not Meaningful
V = Volatile, = Company is on the Priority Stock List

Ticker	ALDR
Price (06/02/2014)	$11.11
52-Week Range:	$9-11
Shares Outstanding: (MM)	29.9
Market Cap.: (MM)	$332.2
S&P 500:	1,922.71
Avg. Daily Vol.:	0
Dividend/Yield:	$0.00/0.0%
LT Debt: (MM)	$0.0
LT Debt/Total Cap.:	0.0%
ROE:	NM
3-5 Yr. Est. Growth Rate:	NM
CY 2014 Est. P/E-to-Growth:	NM
Last Reporting Date:	01/01/2014

Source: Company Data, Wells Fargo Securities, LLC estimates, and Reuters

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Please see page 34 for rating definitions, important disclosures and required analyst certifications
All estimates/forecasts are as of 06/02/14 unless otherwise stated.

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Company Description

Alder Biopharmaceuticals, based in Bothell, Washington, is a clinical stage biopharmaceutical company with differentiated antibody discovery and manufacturing platform to design and select antibodies that have the potential to maximize efficacy in various therapeutic indications including inflammatory and neurological conditions. Additionally, the company's proprietary manufacturing platform, MabXpress, has potential to streamline the manufacturing process compared with the more traditional biologics manufacturing systems, potentially resulting in faster, more scalable, and more cost effective. The company's lead and wholly-owned program, ALD403, is in ph.II and the clinical data thus far supports strong treatment effect in treating migraine. Clazakizumab (anti-IL-6 antibody) is partnered with BMY and it is currently undergoing studies in ph.II for RA and psoriatic arthritis. The company has 4 additional programs in preclinical stage expected to enter the clinic in the future.

Investment Thesis

We have initiated coverage of Alder Biopharmaceuticals with an Outperform rating and a $22-24 valuation range. We believe the company's two lead assets, ALD403 for migraine and Clazakizumab for autoimmune diseases, both have strong efficacy/safety profiles, clear paths to approval, and blockbuster potential. We believe ALDR shares considerably undervalue the future milestone, royalty, and sales revenue the two agents could generate, and expect appreciation for the stock as the programs progress.

With ALD403, we believe Alder has the opportunity to be on the leading edge of a significant shift in the treatment of migraine, which could drive considerable long-term value. There are believed to be 36 million people in the United States who suffer from migraine headaches, and while the triptan class of drugs effectively helps shorten and ameliorate episodes, prevention of migraines from occurring would be a significant step forward for many who suffer from frequent attacks. Prophylactic options have been limited to Botox, relegated to the more severe cases and cumbersome to administer, and older, repurposed oral drugs with non-optimal efficacy and safety. Alder's ALD403 is part of an emerging class of prophylactic therapies, antibodies against CGRP, a vasoactive protein also believed to modulate the sensation of pain in migraines. In a recently reported pilot study, ALD403 led to significant reductions in headache frequency compared to placebo, with a group of patients becoming completely headache-free; data from a competing antibody from Lilly at a similar stage of development appeared comparable, corroborating the treatment effects with such a mechanistic approach are likely real. Safety of Alder's antibody (as well as Lilly's) has appeared clean, suggesting that antibodies to CGRP will not share the same liver toxicity problem that led to the discontinuation of small molecule CGRP antagonists that had been explored in the past. Though additional studies will be needed to optimize dose and delivery, including determining the right administration frequency if the antibody were given subcutaneously (SC), we believe the data to date suggest a good probability that ALD403 will ultimately reach the market, assuming safety remains clean, particularly given that headache frequency -- where the drug already showed clear benefits -- is a registrational endpoint in migraine prevention.

We see blockbuster potential for ALD403 despite the presence of competitors, with potential for meaningful operating leverage. The development space among anti-CGRP antibodies is becoming crowded, with three other antibodies at similar stages; Alder's is among the furthest along to have demonstrated positive proof of concept, though several of the other companies have greater developmental and commercial resources than Alder, which will likely make it a competitive race. Still, in the end, based on our physician feedback, we believe antibodies designed specifically for migraine prevention, with efficacy and safety properties ALD403 has demonstrated, would get significant adoption into a large market we see as capable of supporting multiple potential entrants. Even with what we believe are very achievable 4-5% penetration rates among high-frequency and chronic migraneurs treated with prophylaxis, we believe the market opportunity could exceed $1.4 billion in just the fourth year of launch (2023E). Alder would also likely be able to sell the drug itself in the United States and would likely incur very low cost of goods given its high-efficiency antibody production platform, enabling the company to extract significant value from the agent.

We believe Clazakizumab could be a competitive entrant in the very large rheumatoid arthritis (RA)/psoriatic arthritis (PsA) space, helping generate meaningful milestone and royalty revenue for Alder. Clazakizumab is an anti-IL-6 antibody completing phase II development in RA and also being explored in PsA. Targeting the IL-6 pathway in autoimmune diseases has been well validated by the success of Roche's Actemra, which sells more than $1 billion annually. And in nine clinical studies, including a recently reported head-to-head study versus leading biologic Humira, Clazakizumab has demonstrated response rates competitive with other biologics in RA patients with safety comparable to Actemra. The commercial and development space for RA biologics is very crowded (and as such, the regulatory bar high), and several other IL-6 targeted agents are in late-stage development. Still, Clazakizumab appears to have several features we believe could resonate well in the market, including some evidence it produces higher remission rates than other drugs, which should be appreciated by clinicians as they set higher goals for patient

outcomes, with a long half-life enabling monthly delivery. Our physician suggests that a new agent like Clazakizumab is unlikely to replace the entrenched anti-TNF agents used extensively in RA patients failing DMARDs; however, with RA patients often cycling through multiple therapies, growing rheumatologist experience with IL-6 targeted agents, Clazakizumab's differentiating features potentially adding up to a best-in-class non-TNF biologic, and partner Bristol-Myers Squibb's considerable development and commercial experience in the space, we believe Clazakizumab is likely to be approved and adopted. Even with use primarily in TNF failures and uptake a fraction of that of the market leader, we believe Clazakizumab could still generate worldwide sales of $1.5 billion by 2023, potentially providing royalties to Alder of more than $250 million. In addition to sales royalties, Alder also stands to gain nearly $400 million in development and regulatory milestones in RA alone, which, given our view that Clazakizumab is highly likely to succeed in phase III, we believe will provide a key source of non-dilutive funding over the next several years--and themselves even exceed the company's current market cap.

Valuation

We have established a $22-24 valuation range for Alder. We based our valuation analysis on our probability-adjusted revenue projections for ALD403 in migraine and Clazakizumab in RA and PsA. We assume a 25% probability of success for ALD403, given that the drug is early stage and the class is new, balancing that with the very promising initial signals of activity. We assume a 70% probability of success for Clazakizumab in autoimmune indications, which we believe is appropriate given the extensive efficacy and safety data, clear path to approval in these indications, and generally validated mechanism of action. Assuming approximately 45 million diluted shares outstanding, which accounts for a potentially dilutive capital raise between now and the launch of these drugs, but also assumes some receipt of milestones and a potential up-front payment for ALD403, we arrive at a probability-adjusted 2020 EPS estimate of $2.11. Applying a 30x multiple, which we believe is appropriate for a company of Alder's size and potential, and discounting back 15% for approximately five and a half years, yields a per share valuation of $29. Using a valuation analysis based on sales multiples, using a 3x multiple (which accounts for the sales blend between ALD403, which the company will likely sell itself in the United States, and Clazakizumab, on which the company receives royalties, as well as accounting for the fact that this year would likely substantially precede ALD403's peak sales period), and discounting back at 12% would yield a potential valuation of $18. Combining these two methodologies, we believe our valuation range of $22-24 is appropriate.

Exhibit 1. Valuation Analysis

Year:	**2020E**	**Discount (yrs)**	**5.6**	**EPS:**	**$4.84**	**Shares out:**	**45,339**
Product:	Indication:	Region	Probability of success:	Sales (MM)	Net to company:	EPS contribution:	Probability-weighted EPS contribution:
ALD403	Migraine	WW	25%	$311	41%	$2.82	$0.70
Clazakizumab	RA, PsA	WW	70%	$605	15%	$2.00	$1.40
Total			Prob-weighted sales	$501		$4.82	$2.11

	Discount Rate:				
EPS Multiple:	5%	10%	15%	20%	25%
15	$24	$19	$14	$11	$9
20	$32	$25	$19	$15	$12
25	$40	$31	$24	$19	$15
30	$48	$37	$29	$23	$18
35	$56	$43	$34	$27	$21
40	$64	$49	$39	$30	$24

	Discount Rate:				
Sales Multiple:	10%	11%	12%	13%	14%
2	$13	$12	$12	$11	$11
3	$19	$19	$18	$17	$16
4	$26	$25	$23	$22	$21

Source: Wells Fargo Securities, LLC estimates

Upcoming Milestones and Product Pipeline

Exhibit 2. Upcoming milestones

Product	Event	Timeline
ALD403	Finalize ph.IIb plan in dialogue with FDA	2H14
	Initiate ph.IIb dose-ranging study in high-frequency migraine	4Q14
	Complete enrollment in ph.IIb	mid-2015
	Data from ph.IIb study	end-2015
	Potentially initiate ph.III program	mid-2016
	Potentially initiate ph.IIb SC study	2H15
	Initiate ph.III program for IV	2H16
	Initiate ph.III program for SC	2017
	Potential ph.III data	2017/2018
Clazakizumab	Completed dose-ranging ph.IIb RA study	4Q14
	Potential publication of previously-presented ph.II RA study	4Q14
	Presentation of ph.IIb dose-ranging RA data	Mid-2015 (EULAR)
	Initiation of ph.III program	2015
	Potential presentation of ph.II psoriatic arthritis data	4Q14 (ACR)

Source: Company reports and Wells Fargo Securities, LLC estimates

Exhibit 3. Product pipeline

Product (partner)	Indication/mechanism	Status
ALD403	Migraine (anti-CGRP antibody)	Phase II
Clazakizumab	RA, psoriatic arthritis (anti-IL-6 antibody)	Phase II

Source: Company reports and Wells Fargo Securities, LLC

Key Risks

Clinical Development Risk. ALD403 is relatively early stage, having been in phase I development and one proof-of-concept phase II study. On the efficacy side, it is possible that the promising migraine prevention results observed in phase II will not be replicated in larger studies, especially given the tendency of these studies to show a high placebo effect and the more modest benefits when results are looked at in terms of mean reductions in headache days. Although LFT elevations observed with small molecule approaches to CGRP inhibition do not appear to be an issue with anti-CGRP antibodies, there is still a risk that this or other side effects could emerge over multiple doses in larger studies, which could preclude future regulatory approval or commercial viability. It could be important for Alder to succeed in developing a subcutaneous form of ALD403 in order to maximize its competitive positioning, and though a SC was tested in phase I, the company has not yet demonstrated proof of concept yet with an SC-administered ALD403. The drug has also not yet been tested in chronic migraine; failure to replicate the promising efficacy in chronic migraine patients could result in a less favorable label and reduce the market opportunity. Regarding Clazakizumab, partner BMY and Alder still need to conduct an additional study in order to optimize the dose, given that there was no clear dose dependence; and if activity at the overlapping doses does not replicate prior data, it could call into question the validity of the promising phase IIb data previously reported. It may be important for future clinical studies of Clazakizumab to confirm the potential remission advantages over other therapies in order to optimize its competitive positioning.

Commercial Risk. Both of Alder's products would potentially enter crowded competitive markets, presenting commercial risk. There are several other companies developing anti-CGRP antibodies for migraine, with differences between the programs not entirely elicited at this point. Subtle nuances like dosing and administration differences could ultimately result in significant differences in adoption between anti-CGRP antibodies for migraine, and these likely will not become apparent until programs from Alder and competitors move forward further in clinical development. Alder intends to market '403 on its own in the United States, which, while potentially maximizing profit, would require considerable investment; additionally, the company does not have any commercial experience, and would potentially be competing with others, like Amgen and Lilly, with considerable experience and large infrastructures. Generic agents are currently used in migraine prophylaxis, and though these have efficacy and safety limitations, it is not unreasonable to expect insurers to require patients try such therapies first before moving on to more expensive therapies like '403, which could reduce '403's ultimate market opportunity. Given that the anti-CGRP antibodies could be the first class of drugs specifically designed for migraine prophylaxis, the ultimate market has not yet been established and there is a risk that such drugs will not be embraced as broadly as expected, which would reduce '403's revenue potential. Regarding Clazakizumab, there are numerous biologics for RA and similar autoimmune diseases well entrenched in the market, and multiple other therapies, including those targeting IL-6, in late-stage clinical development. Although the market size is large, as multiple additional therapies potentially reach the market, the ultimate opportunity for Clazakizumab could become smaller, making it even more important for Clazakizumab to continue to demonstrate properties that incrementally differentiate it from other therapies.

Regulatory Risk. Given the large number of migraine and RA/PsA patients potentially served by ALD403 and Clazakizumab, respectively, the FDA and EMA would likely require large phase III programs for both agents. Competition in both spaces could potentially slow pivotal study enrollment, which would delay potential approvability and revenue to Alder. The bar for safety for both drugs would likely be very high, and any unforeseen toxicity issue emerging with either agent could meaningfully reduce the likelihood of approval.

Financing Risk. We would not expect Clazakizumab and ALD403 to reach the market until the 2018-19 time frame, potentially leading to sustainable profitability for Alder by 2020. We believe milestones from the BMY collaboration on Clazakizumab should help Alder cover future development costs, as could a potential up-front payment for ex-U.S. rights to ALD403. However, until such milestones/payments are received, and in the case that they are not received, Alder will likely need to raise additional capital through secondary stock and/or convertible debt offerings to support the additional development of their candidates, which could lead to dilution of existing shareholders.

Developmental Programs

ALD403

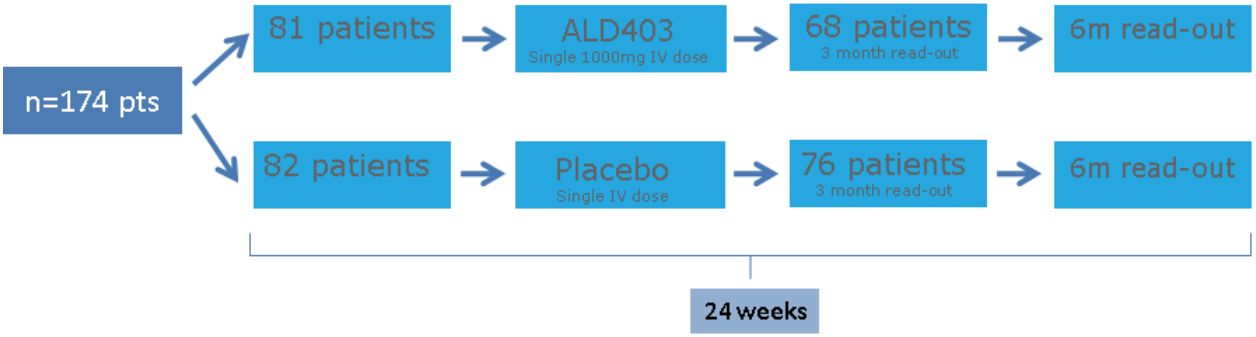
Overview

ALD403 is a monoclonal antibody against CGRP in phase II development for the prevention of migraines. Calcitonin gene-related peptide (CGRP) is a small protein that modulates the dilation of blood vessels and has been implicated in the sensation of pain in migraine headaches. We view CGRP antagonism as offering some of the most exciting potential for migraine prophylaxis as it directly targets a modulator of the incipient cause of migraine headache. Although it represents a new approach to the prevention of migraines, CGRP has been very well studied in migraine pathophysiology, with nearly 600 citations retrieved in a literature search on PubMed for basic and clinical science reports on migraine and CGRP. Alder recently completed an initial phase II proof-of-concept study for the antibody and expects to start a phase IIb study assessing a broad range of doses in fall 2014.

Clinical efficacy

We believe 403 demonstrated clear, durable, convincing efficacy in a recently-reported phase II proof of concept study. The randomized, double-blinded, placebo-controlled phase II study, which was presented May 2 at the American Academy of Neurology (AAN) annual meeting, enrolled a total of 163 patients, who at baseline suffered from 5-14 migraine days per month (mean of 9-10 migraine days per month). ALD403 was administered as a single 1,000mg IV dose, versus a control arm where subjects received an IV dose of placebo. The primary endpoint was measured during weeks 5-8 as the mean change in migraine days per month from baseline (see Exhibit 4).

Exhibit 4. Design of '403 phase II proof-of-concept study

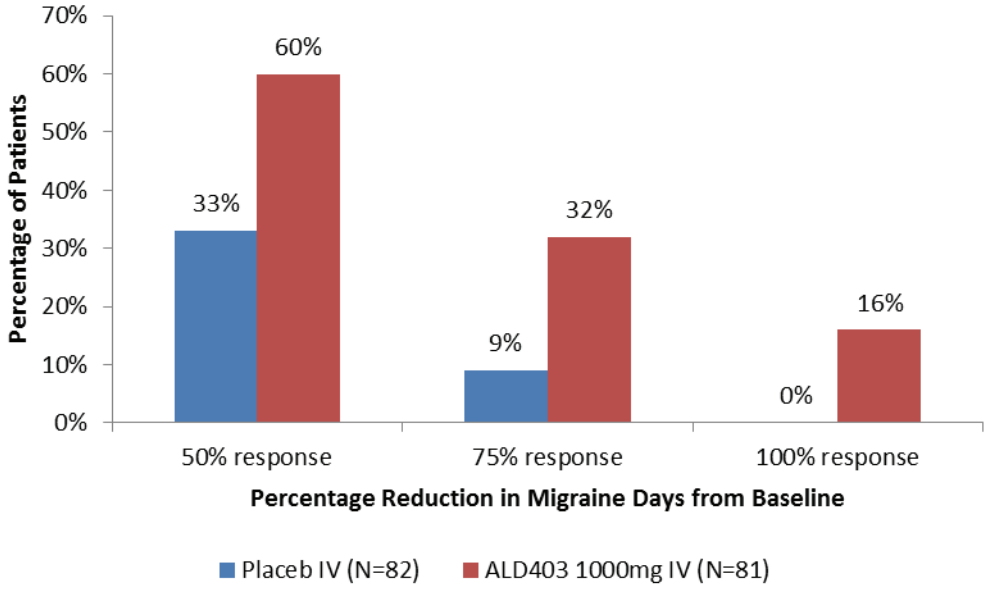


Source: Goadsby P et al, AAN 2014; and Wells Fargo Securities, LLC

Frequency of headache days is the FDA's accepted registrational endpoint based on past approvals of topiramate and Botox for migraine, which we believe lessens development risk.

The drug produced notable increases in the proportions of patients with meaningful reductions in their number of headache days. A responder analysis was conducted, in which the percentage of patients in each arm who experienced 50%, 75%, and 100% reductions in migraine days from baseline over the three-month period were calculated. We note that such responder analyses have been used as prior registrational endpoints in both pharmacologic therapies and medical device treatments for migraine, and the FDA has already confirmed to Alder that a responder analysis would be an acceptable way of assessing the pivotal endpoint for '403. At those thresholds, 60% of treatment patients saw a 50% reduction, versus 33% of controls ($p<0.001$), and 32% of treatment patients saw a 75% reduction versus 9% of controls ($p<0.001$). Perhaps most impressively, 16% of patients (versus 0% for placebo) had a "complete response," meaning they experienced zero headaches (see Exhibit 5).

Exhibit 5. ALD403 produced meaningful increases in the number of responders with fewer headache days

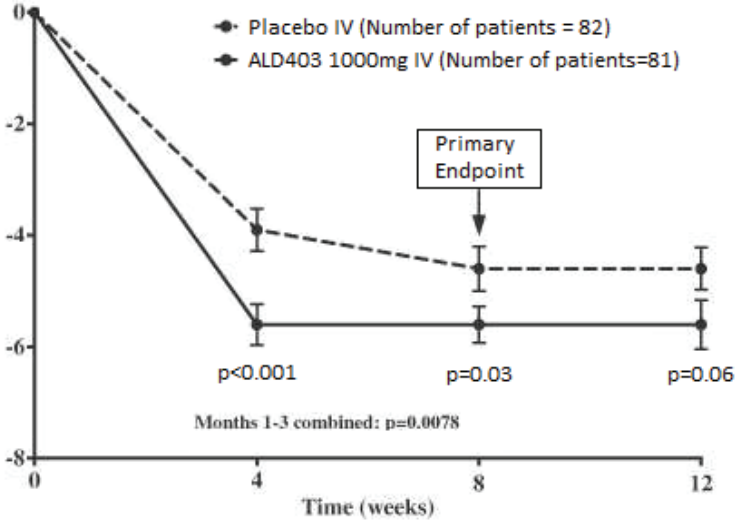


Source: Adapted from data in Alder BioPharmaceuticals S-1, and Wells Fargo Securities, LLC

We believe an agent with such a response rate would be embraced by clinicians as KOL feedback suggested to us that if '403 were to work robustly in only one-third of migraneurs, given the degree to which this would improve their functioning and well-being, demand would be strong.

The mean reductions in headache days for the whole treatment group were less robust, but still demonstrated clear signs of efficacy that were statistically significant, and with only a single dose. While both arms experienced improvement, treatment with '403 demonstrated a mean reduction of 1.0 days over placebo between weeks 5-8 and baseline (absolute improvement of 5.6 days versus 4.6 days by placebo, one-tailed p=0.03) (see Exhibit 6).

Exhibit 6. Mean change in headache days on treatment by '403 versus placebo over three months



Source: Alder BioPharmaceuticals S-1 (used with permission), and Wells Fargo Securities, LLC

Although placebo effects tend to be high in migraine studies and this was no exception, the fact that the mean reductions in headache days reached statistical significance at the 4- and 8-week time-points, and nearly so at

the 12-week time-point, despite the relatively modest study size, we believe provides corroboration of a true treatment effect. We believe the responder analysis better depicts the clinical meaningfulness of the drug's effect size, but note that the mean reductions in headache days could be further improved with multiple doses (as this study was only a single dose), or with a better understanding of how to enrich for responders (although predictors of response are not yet understood). Severity of headache was not dramatically improved (-0.2 versus -0.1 placebo), though not surprising given the mechanism is geared more for prophylaxis of migraines through blocking CGRP, rather than acting directly on the nociceptive pathway that mediates the intensity of migraine headache.

Recently reported data from LLY's anti-CGRP antibody, in our view, provides validation of the target and approach for prophylaxis. Data from the phase II program for LLY's LY2951742 from Lilly was also presented in the same AAN session. Lilly's trial was similarly randomized, double-blinded, and placebo controlled, and enrolled 217 patients with 4-14 migraine days per month. The primary endpoint was mean change in the frequency of headache days, measured slightly differently (weeks 9-12 versus baseline), and rather than a single IV dose, patients received 150mg SC every two weeks for three months. Treatment by LY2951742 demonstrated a mean improvement of 1.2 days over placebo at three months (absolute improvement of 4.2 days, versus 3.0 days by placebo, p<0.01), similar to ALD403. Moreover, improvements in LY2951742-treated patients were also observed in the number of migraine headaches (p<0.0117), number of migraine attacks (P<0.0051), and responder rate (odds ratio = 2.88 [confidence interval 1.74-4.69]). While there were differences in the in the frequency and mode of administration (LY2951742 was administered as biweekly subcutaneous injections of 150mg doses), and subtle differences between the antibodies themselves, we see the data from LY2951742 as helping to corroborate the clinical activity and mechanism of action of anti-CGRP biologics on prevention of migraines.

Safety data

Safety was notably extremely clean at the single dose that demonstrated efficacy. The drug appeared well tolerated, with no differences in the phase II in the types or frequency of AEs (56% '403, versus 50% placebo), vital signs, or lab results between the groups. The presenter noted that there were no elevations in LFTs. This was further evidence that the liver toxicity that had plagued Merck's small molecule antagonist of CGRP, whose development was discontinued because of this side effect, was a drug-related rather than target-related issue. Additionally, no blood pressure, heart rate, or EKG changes were observed and there were no infusion reactions. The only AE mentioned that occurred at higher frequency was tooth abscess (three cases with '403, versus 0 in placebo), which the investigator told us he did not believe was drug related; arthralgia was higher for placebo (one case with '403, versus four for placebo). Of course, the safety profile of '403 remains to be confirmed in larger studies involving multiple doses, though the lack of any safety signal at a dose that provided clinically meaningful efficacy is reassuring.

The clean profile of LLY's anti-CGRP antibody LY2951742 also provides reassurance about the safety of the mechanistic approach. While patients on LLY's drug had incrementally higher rates of respiratory infections and abdominal pain/discomfort versus placebo and there were some injection site reactions, overall we believe it corroborates the general safety of the CGRP approach itself and may reduce the likelihood an unexpected safety issue emerges with '403.

Prior Clinical Studies

Earlier clinical studies of '403 demonstrated good safety and favorable pharmacokinetics, which should bode well for future trials. In a three-part phase I clinical study, Alder evaluated the safety, PK, and pharmacodynamics (PD) of intravenous (IV) '403 as single treatment and as a combo with triptans (the current dominant standard of care treatment for interruption of low frequency migraines), and finally, evaluated the bioavailability and pharmacodynamic effect of subcutaneous versus IV dosed '403.

- **Clean safety.** In the initial phase I, the drug was safe and well tolerated across all tested dose levels (1-1,000mg), with no differences compared to placebo, and notably no LFT signals.

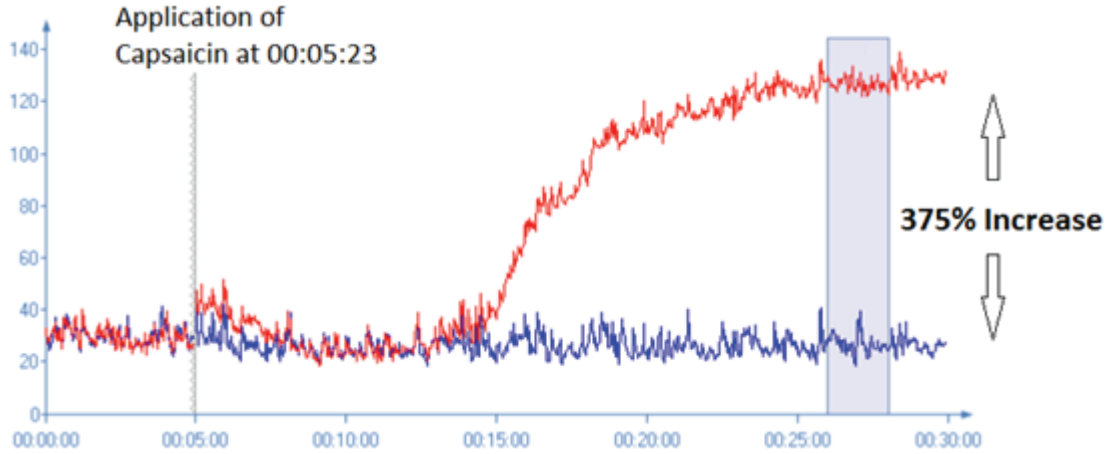
- **Well-behaved PK.** The drug also demonstrated a half-life of approximately 28-32 days at the 1,000mg dose, and plasma concentration of the drug increased with higher dose levels, suggesting linear PK.

- **Combines well with triptans.** In combination with triptans, '403 also proved to be well-tolerated and without any notable safety signals. No increases in systolic or diastolic blood pressure or in the other parameters evaluated in single-agent triptan use were demonstrated, which we believe is important, as migraine patients taking '403 for prophylaxis would likely still be taking triptans for acute headache treatment. While triptans alone are already considered a very safe class of medications, their risk of serotonin syndrome, a highly adverse metabolic interaction associated with use of small molecule

inhibitors of the cytochrome P450 system, could actually be avoided with use of '403, whose elimination pathway, though not yet well-defined, is likely via proteases, instead of by hepatic metabolism.

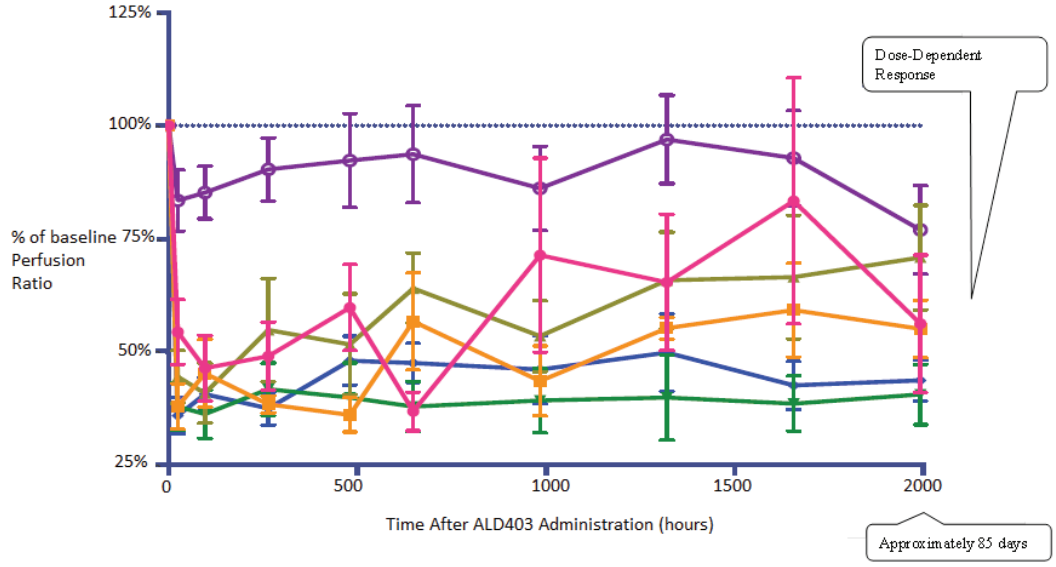
- **PD supports mechanism.** The PD effects of IV '403 were also characterized in a study of the inhibitory effect of vasodilation of a gradient of '403 dosage levels, and we believe provide good support for the mechanism by which the drug reduced migraine frequency in phase II. The clinical PD model was constructed using vasodilation induced by dermal application of topical capsaicin, which mediates the release of CGRP from capsaicin-sensitive vasodilator nerves. It was found that '403 dosage levels down to 300mg produced a complete and durable suppression of CGRP-induced vasodilation (up to 84 days post-treatment), with suppression rates beginning to fall at the 100mg and 30mg dose levels. (see Exhibits 7 and 8).

Exhibit 7. Increases in Dermal Blood-flow from Capsaicin-induced Vasodilation



Source: Alder Biopharmaceuticals (used with permission) Wells Fargo Securities, LLC

Exhibit 8. Durable Inhibition of Vasodilation in a Dose-Ranging '403 Clinical Study

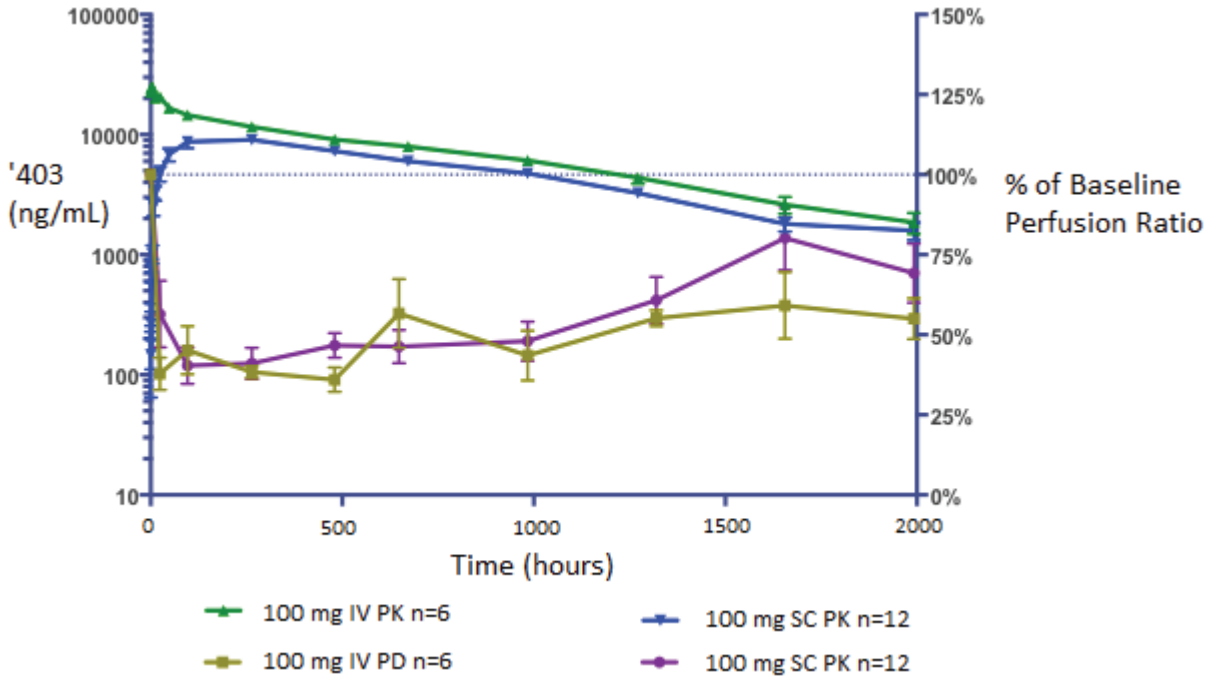


Source: Alder Biopharmaceuticals (used with permission), Wells Fargo Securities, LLC

The imaging of blood flow was initially measured using Doppler imaging, which we view as a well-validated, reliable, non-invasive method of characterizing microvascular changes. And capsaicin-induction of vasodilation has also been well validated as a reproducible means of analyzing changes in vascular flow. This method was later replaced by laser speckle contrast imaging, which has also been well validated in the literature as possessing high quantitative accuracy of blood flow measurement.

- **SC viability.** Finally, the phase I trial elucidated that subcutaneously-delivered '403 had good bioavailability (70-72%) compared to the IV delivery, with a PD effect that was similar to that of IV in magnitude and duration, supporting the potential of the drug to be dosed subcutaneously in the future (Exhibit 9).

Exhibit 9. SC formulation of '403 shows high bioavailability versus IV



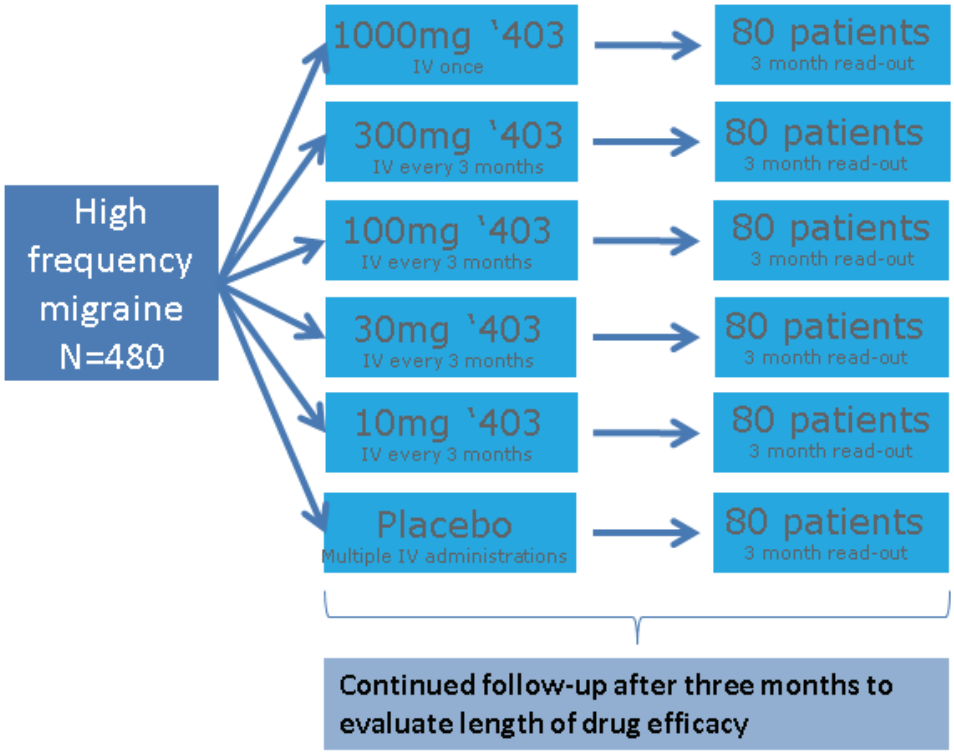
Source: Alder BioPharmaceuticals (pg. 76 of S-1; used with permission), and Wells Fargo Securities, LLC

The exposure profiles following SC drug administration illustrate '403 levels with bioavailability (AUC) values within 72% of those measured following IV administration. '403 appeared to have a slow terminal elimination phase after IV administration (half-life of 32 days in the 1,000mg dose), helping explain the long duration of clinical benefits observed in phase II. SC-administered '403 had relatively rapid absorption, though suppression took slightly longer than for the IV form; this could suggest one approach to optimize convenience and rapidity of response could be use of an IV loading dose, followed by SC maintenance dosing. Given that full suppression in the PD study was achieved on 300mg, and even the 100mg IV dose level performed relatively well, we anticipate that the dose-ranging study with dose levels around the ED50 should enable better characterization of the shape of the dose-response curve. Notably, the company informed us of the absence of observed injection site reactions (unlike with LLY's SC antibody).

Future plans

With proof of concept now in hand, we believe it will be critical for Alder to quickly hone in on the optimal dose, route of administration, and frequency of administration, of '403, given a competitive landscape with multiple anti-CGRP biologic pipeline candidates. The next step is for ALDR to start a phase IIb trial, expected in Q4 2014, following completion of FDA discussions. The company plans a dose-ranging, double-blind, randomized, placebo-controlled trial of IV '403 in patients with high-frequency migraines (5-14 migraines/month), similar to the initial proof-of-concept study. The objective in this study is to select an appropriate dose level and frequency for phase III (and for future subcutaneous studies) and determine whether lower doses can potentially be equally effective. The company plans to study five dose levels (1,000mg, 300mg, 100mg, 30mg, and 10mg) versus placebo) with various frequencies of administration. Endpoints would be similar to those in the phase IIa: change in mean migraine days per month from baseline, and patients seeing 50%, 75%, and 100% improvements in migraine days per month. We would expect the 1,000mg and 300mg doses to show good efficacy, the 100mg to have lesser durability, and the lower two doses to be sub-therapeutic or show an incomplete response. The proposed trial design is depicted in Exhibit 10.

Exhibit 10. Potential phase IIb dose-ranging trial design



Source: Alder BioPharmaceuticals Research Overview, and Wells Fargo Securities, LLC

The trial is to be conducted across 50 centers and Alder hopes to complete enrollment mid-2015, with data, end-2015. While proof of concept is already in hand, we believe additional data corroborating efficacy and safety would still serve as a potential de-risking catalyst for the program and the stock. The study should also enable selection of a clinically useful SC dose.

Though the feedback we have received suggests there could be a role for IV formulations, and neurologists and certain patients should be reasonably comfortable with the approach, we believe subcutaneous formulations would provide important enhancements to convenience. Since patient preferences for route of administration are central to uptake and adherence, we believe a subcutaneous injection formulation would increase '403's commercial potential. Alder plans to test a subcutaneously delivered '403 in dose-ranging studies once a suitable dose is found in the phase IIb. We believe that even if dosing on the higher end appears necessary, Alder would be able to deliver the agent in an acceptable SC form and volume. Assuming 300mg IV every three months is effective, we believe the company could formulate 100mg into a SC injection of no more than 1mL to be administered monthly and could potentially go higher.

A phase III program would likely be large and could begin as early as 2016. In a pivotal program, we expect Alder would need to have at least 1,000-1,500 patients exposed to '403 for 3-6 months. We believe a program would be structured as two phase IIIs, each 6-12 months in duration, in high-frequency migraine patients. Based on the proof-of-concept study this year, we view the risk of '403 inactivity in such studies as low, especially given that the endpoint, changes in migraine days, would likely be essentially the same as what has been previously tested. We are also optimistic that despite the smaller size of the early studies, '403 as an antibody will continue to demonstrate limited off-target toxicity. Ancillary studies within the phase III program may also be necessary, such as studies in patients with hypertension, or studies to assess embryo-fetal abnormalities given the nature of the target population. It will be important for Alder to conduct a large enough phase III program not only to satisfy regulatory requirements, but to generate comparable safety data to some of the other large companies pursuing anti-CGRP antibodies, to optimally compete in the market.

Chronic migraneurs could also be tested as part of a pivotal program, to maximize the breadth of the label. Alder could also conduct a phase III study in chronic migraneurs, who are defined as having more than 15 headaches per month. We see high potential for '403 to prevent migraines in chronic migraneurs, as there is no mechanistic reason in our view why '403 could not work in chronic migraine, and there were no differences in efficacy among patients at the higher end of the 5-14 headaches/month spectrum in phase II.

This potential for the broadest possible label would likely hold important commercial implications among the many clinicians who believe that patients with high-frequency episodic migraine eventually demonstrate progression to chronic migraines. One of the most popular treatments for chronic migraines now is Botox, which requires a series of 31 injections throughout the head and neck and causes neck pain in up to 9% of patients (versus 3% in placebo in trials). With '403's safety profile, we believe with further success in clinical development and approval, the drug will likely be positioned competitively against Botox.

We believe phase III trials could start 2016 upon positive phase IIb data, and could be complete by 2018, at least for the IV formulation; SC may be important to accelerate. While both formulations would be tested, the focus will be primarily on the IV formulation, and then followed by the subcutaneous formulation, though we believe the company would be well served by accelerating development of the latter to ensure all possible avenues of delivery given the competitive space it is entering.

Market opportunity

We believe there are a substantial number of individuals who could be treated with an effective and safety migraine prophylaxis drug. While estimates of migraine epidemiology vary, the Migraine Research Foundation estimates that approximately 36 million in the United States suffer from migraines, with approximately 86% diagnosed, or 22.3 million. Reports in the literature generally report a distribution of 8% of patients as chronic migraneurs, suffering more than 15 headaches days per month, 35% as high frequency, suffering 5-14 migraine days per month, and 57% as low frequency, suffering four or less migraine days per month.

Current abortive therapies are effective, but do not prevent headaches from occurring and have other limitations. Currently available abortive therapies include the earlier-discussed triptans, as well as non-steroidal anti-inflammatory drugs, and anti-emetic/dopamine receptor antagonists, as well as combinations of these classes. While each medication class has contraindications in certain patient subsets, acute treatments are limited more generally in several ways. First, the treatments tend to work earlier in the course of migraine treatment, with extended use leading to migraine recurrence and overuse causing medication overuse headache. Second, migraines can induce a gastric stasis phenomenon that causes poor absorption of oral drugs, rendering them less effective in a prolonged migraine attack. Prophylactic treatment can play an important role in avoiding both of these effects.

While there are several available options for migraine prophylaxis, some of which are generic, their efficacy and safety is non-optimal, or they are cumbersome to administer, opening the door for new therapies like anti-CGRP antibodies. Current oral prophylactic options include beta-blockers, anti-depressants, and anti-convulsants. While these are now commonly used because of the need for prophylaxis, side effects such as nausea, fatigue, sleep cycle disruption and mild decline in cognitive abilities significantly limit their tolerance. For example, it is thought only 10% of patients on topiramate, an anticonvulsant approved for migraine prophylaxis, are still on the drug after one year. Botox, also approved for migraine prophylaxis, requires multiple injections, making it an inconvenient choice for some. Efficacy is also limited; the response rate to Botox in the treatment of migraine has generally ranged from 30% to 50% (though this varies further, depending on how patients are stratified), and for topiramate, 40-60%, though interpreting such studies cleanly is also difficult as they were generally complicated by high placebo response rates. In the particular case of topiramate, the efficacy may have been skewed by dropouts given the relatively high side effects burden. Historical dropout rates were approximately 50% in the first six months of migraine trials, as the primary analyses were performed on a last observation carry forward basis. While we hesitate to compare results across trials directly, these rates suggest significant opportunity for adoption of, and persistence with, a prophylactic with the 50%, 75%, and 100% responder rates seen with '403, with a benign side-effect profile. Clinicians we spoke with also appreciated the concept of prophylactic drugs specifically designed for migraine, which avoid some of the "stigma" attached to the other medications currently used.

We believe the market opportunity for '403 could be $1.4B by 2023, with most sales in the United States. We model sales in the United States and Europe only (see Exhibit 11). Alder plans to build a 70-100 person U.S. sales force, and we model out-licensing to a pharma player more established in Europe given the formidable challenges in commercializing a drug for the European migraine market. By 2023, we estimate a U.S. and EU population size of 338M and 517M, respectively. We assume the migraine prevalence pool remains unchanged as a proportion of the overall population (11.7% in the United States, 14% in the European Union). We model migraine diagnosis rates increasing slightly worldwide over time, with expanded access to care under the ACA and growing public awareness and attention to migraine headaches should increase consults to clinicians/headache specialists. We model single-digit penetration rates in both high-frequency migraine and chronic migraines (slightly higher in chronic migraines) across the United States and European Union, and no adoption of '403 among low-frequency migraneurs. This allows for the possibility of some insurers installing step edits, as with Botox, so that generic drugs are first trialed (though we do not see this as a significant hurdle given their low persistence rates), as well as the availability of competing anti-CGRP antibodies. We model an annual price of '403 of $8,000 in the United States by launch, a slight premium to where we expect Botox to be priced at that point, with a lower price in Europe.

Exhibit 11. Revenue build for ALD403 in migraine

		2019	2020	2021	2022	2023
United States	Overall population	328,562,069	330,862,004	333,178,038	335,510,284	337,858,856
	Migraine prevalence pool	38,441,762	38,710,854	38,981,830	39,254,703	39,529,486
	Clinically diagnosed (%)	62.5%	62.6%	62.7%	62.8%	62.9%
	Total number diagnosed	24,026,101	24,232,995	24,441,608	24,651,954	24,864,047
	Clinically treated (%)	28.9%	29.1%	29.3%	29.5%	29.7%
	Total number treated w/ prophylaxis	6,943,698	7,051,957	7,161,548	7,272,485	7,384,782
	Chronic Migraine (≥15 HA days/month) (%)	7.7%	7.7%	7.7%	7.7%	7.7%
	Chronic Migraine patients	534,665	543,001	551,439	559,981	568,628
	ALD403 penetration (%)	*0.7%*	*1.5%*	*2.7%*	*3.9%*	*5.1%*
	CM Migraine patients treated	3,743	8,145	14,889	21,839	29,000
	High-freq. Episodic Migraine (5-14 HA days/month) (%)	35.0%	35.0%	35.0%	35.0%	35.0%
	High-frequency Migraine patients	2,430,294	2,468,185	2,506,542	2,545,370	2,584,674
	ALD403 penetration (%)	*0.4%*	*1.2%*	*2.2%*	*3.2%*	*4.2%*
	HF Migraine patients treated	9,721	29,618	55,144	81,452	108,556
	Low-freq. Episodic Migraine (0-4 HA days/month) (%)	57.3%	57.3%	57.3%	57.3%	57.3%
	Low-frequency Migraine patients	3,978,739	4,040,772	4,103,567	4,167,134	4,231,480
	ALD403 penetration (%)	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	LF Migraine patients treated	0	0	0	0	0
	Total migraine patients on ALD403	13,464	37,763	70,033	103,291	137,556
	Annual price	$8,000	$8,240	$8,487	$8,741	$9,004
	Compliance	85.0%	85.0%	85.0%	85.0%	85.0%
	US ALD403 sales	**$91,549,001**	**$264,479,104**	**$505,197,048**	**$767,466,759**	**$1,052,723,864**
Europe	Overall population	513,139,488	514,365,687	515,314,370	516,263,053	517,211,737
	Migraine prevalence pool	71,839,528	72,011,196	72,144,012	72,276,827	72,409,643
	Clinically diagnosed (%)	54.5%	55.0%	55.5%	56.0%	56.5%
	Total number diagnosed	39,152,543	39,606,158	40,039,927	40,475,023	40,911,448
	Clinically treated (%)	28.9%	29.1%	29.3%	29.5%	29.7%
	Total number treated	11,315,337	11,525,647	11,731,956	11,940,392	12,150,963
	Chronic Migraine (≥15 HA days/month) (%)	7.7%	7.7%	7.7%	7.7%	7.7%
	Chronic Migraine patients	871,281	887,475	903,361	919,410	935,624
	ALD403 penetration (%)	*0.0%*	*0.4%*	*0.9%*	*1.6%*	*2.3%*
	CM Migraine patients treated	0	3,727	8,130	14,894	21,894
	High-freq. Episodic Migraine (5-14 HA days/month) (%)	35.0%	35.0%	35.0%	35.0%	35.0%
	High-frequency Migraine patients	3,960,368	4,033,976	4,106,185	4,179,137	4,252,837
	ALD403 penetration (%)	*0.0%*	*0.2%*	*0.7%*	*1.3%*	*1.9%*
	HF Migraine patients treated	0	9,682	29,565	55,165	81,654
	Low-freq. Episodic Migraine (0-4 HA days/month) (%)	57.3%	57.3%	57.3%	57.3%	57.3%
	Low-frequency Migraine patients	6,483,688	6,604,196	6,722,411	6,841,845	6,962,502
	ALD403 penetration (%)	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	LF Migraine patients treated	0	0	0	0	0
	Total migraine patients on ALD403	0	13,409	37,695	70,059	103,548
	Price	$4,000	$4,120	$4,243	$4,371	$4,502
	Compliance	85.0%	85.0%	85.0%	85.0%	85.0%
	EU ALD403 sales	**$0**	**$46,955,512**	**$135,959,823**	**$260,274,100**	**$396,228,706**
	Royalties on EU ALD403 sales	**$0**	**$7,982,437**	**$23,113,170**	**$44,246,597**	**$67,358,880**
	ALD403 Migraine WW sales	**$91,549,001**	**$311,434,615**	**$641,156,871**	**$1,027,740,859**	**$1,448,952,570**
	ALD403 Migraine revenues	**$91,549,001**	**$272,461,541**	**$528,310,218**	**$811,713,356**	**$1,120,082,744**

Source: Wells Fargo Securities, LLC estimates

Competitive landscape

The competitive space in CGRP antibodies has several candidates that we believe will be important to watch in development, both from a competitive and a validation standpoint, though we believe the market would be large enough to support multiple entrants if this new class of anti-CGRP therapeutics alters the treatment paradigm, as we believe it has potential to do. There are currently three other anti-CGRP antibodies in the clinic besides ALD403; these are LY2951742 (Eli Lilly/Arteaus Therapeutics) (discussed previously), LBR-101 (Labrys Biologics, acquired from Pfizer), and AMG-334 (Amgen). With data from only one of these therapies, LLY's, having been reported in patients to date, it is difficult to compare the agents to understand which (if not all) might have the best opportunity for clinical success. Commercially, as larger companies with established sales and marketing infrastructures, Lilly and Amgen would appear to have advantages. Timing-wise, while Amgen is the farthest along in development, it is not clear that the company has yet generated proof-of-concept data; Labrys appears furthest behind in development. The time lines for Alder and Lilly appear to be very similar, with both agents due to enter phase IIb dose-ranging study this year (though the exact timing of which LLY has yet to disclose). According to ClinicalTrials.gov (NCT02104765) LLY plans to start another phase I study (in 44 healthy Japanese and Caucasian patients), but our feedback was that this second phase I study was initiated to study PK relationships across different populations, and there have been no emergent safety concerns nor delays to their phase IIb time lines. A summary of the development status of the competitors is below (see Exhibit 12):

Exhibit 12. Active and Inactive CGRP Programs in Migraine

Drug	Sponsor	Development Stage and Status	Mechanism	Dosing	Trial status
ALD403	Alder	Phase II (Proof-of-concept) – High frequency migraine	CGRP mAb to ligand	Single Dose IV	Completed
		Phase IIb - High frequency migraine, dose-ranging		Quarterly IV or single dose IV	To begin 2H14
LBR101/ PF-04427429/RN-307	Labrys (founded to acquire assets from Pfizer, which has no clawback)	Phase II – High frequency episodic migraine	fully humanized CGRP mAb with little BBB penetrance; targets peripheral inflammatory signalling	Monthly SC x3 months, low vs. high dose vs. placebo	Initiated Jan 2014; ongoing with est. completion January 2015
		Phase II – Chronic Migraine		Monthly SC x3 months, low vs. high dose vs. placebo	Initiated Jan 2014; ongoing with est. completion February 2015
LY2951742	Lilly (Arteaus)	Phase IIa (Proof-of-concept) – Frequent episodic migraine	CGRP mAb to ligand	150mg SC every 2 weeks x3 months	Completed
AMG-334	Amgen	Phase II – Dose-ranging in high frequency migraine	CGRP mAb to receptor	Monthly SC	Data expected end-2014
		Phase II – Dose-ranging in chronic migraine		Monthly SC	Data expected 2015
NOX-L41	Noxxon Pharma	Preclinical	CGRP receptor antagonist		
BI 44370	Boehringer Ingelheim	Suspended			
MK-3207	Merck	Suspended due to liver biomarker abnormalities			
Telcagepant (MK-0974)	Merck	Suspended due to liver biomarker abnormalities			
Ubrogepant (MK-1602)	Merck	Suspended due to liver biomarker abnormalities			
BMS-927711	Bristol-Myers	Suspended			

Source: BioMedTracker, "Review of Migraine" in NeuroPerspectives' April 2014 issue, Wells Fargo Securities, LLC

At this time, based on the data to date, it appears that Alder's and LLY's drugs are comparably effective. Whether this will hold in future studies has yet to be determined, but even with slight differences in dosing, frequency, and administration, both appeared to similarly reduce headache frequency (see Exhibit 13):

Exhibit 13. Comparison of drug and proof-of-concept study characteristics of '403 versus LY2951742

	ALD403	LY2951742
Drug design	Genetically engineered, humanized, anti-CGRP antibody	Fully humanized monoclonal antibody to CGRP
Proof-of-concept trial		
Study Design	Randomized, placebo-controlled	Randomized, placebo-controlled
Route of administration	IV	SC
Dosing	1000mg once	150mg biweekly, over 3 months
Baseline characteristics	5-14 migraine days/month	4-14 migraine days/month
Study size	163 patients, '403 (81) or placebo (82)	217 patients, LY2951742 (107) or placebo (110)
Primary endpoint	Mean change in headache days from baseline at 5-8 weeks	Mean change in headache days from baseline at 12 weeks
Primary outcome	-5.6 days (66%) decrease in migraine days per week ('403) versus -4.6 days (52%) decrease (placebo), p=0.03	-4.2 days (62.5%) decrease in migraine headache days per month (LY2951742) versus -3.0 (42.3%) decrease (placebo), p<0.003
Adverse events in experimental arm versus placebo	There were no major differences in adverse events or lab safety data reported versus placebo	Injection site reactions and pain, upper respiratory tract infections (URIs), and abdominal pain

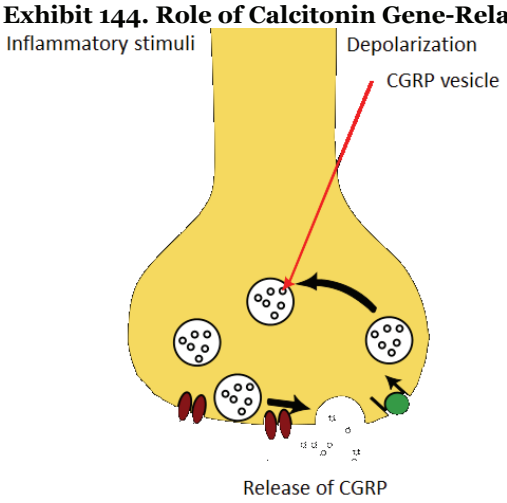
Source: Dodick, D. "CGRP Monoclonal Antibody LY2951742 for the Prevention of Migraine: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study." *American Academy of Neurology Annual Meeting*. May 2, 2014; Goadsby, P., et al. "Randomized, Double-blind, Placebo-controlled Trial of ALD403, an Anti-CGRP Peptide Antibody in the Prevention of Frequent Episodic Migraine." *American Academy of Neurology Annual Meeting*. May 2, 2014.

Though we believe the evolution of the anti-CGRP landscape will be key to watch in the coming years, both for validating of ALD403's biology/safety and for assessing how they might divide the market, but a few features could enable '403 to stand out from the others. Though all the CGRP antagonists in clinical trials currently under way are intended to be long-acting, incremental advantages in dosing intervals could help position any one antibody competitively against the others. The construct of Alder's antibody (lack of glycosylation, etc.) could provide it with potential advantages, though clinical implications of such differences would still need to be demonstrated. Additionally, we believe Alder's approach to targeting the ligand, rather than the receptor will give it an advantage over Amgen, as the CGRP receptor interacts with other factors (and the knockout is lethal), so Amgen's approach could have more safety risks.

Mechanism of action

The mechanism of CGRP inhibition has been extensively evaluated, and we believe the CGRP target has been well validated through decades of migraine headache research. CGRP itself is a 37 amino acid regulatory neuropeptide formed in the cell bodies of sensory neurons of the trigeminal ganglia via alternative splicing of the calcitonin/CGRP gene. During a migraine, the presence of inflammatory stimuli create a depolarizing stimulus in these nerves that cause initial release of CGRP from their peripheral and central terminating processes. The CGRP then acts to stimulate CGRP receptors located throughout the meninges, and precipitates multiple responses, including neurogenic inflammation with mast cell degranulation and plasma extravasation, pain sensation, and vasodilation (see Exhibit 14). Indeed, CGRP levels in the serum appear to correlate directly with the onset of migraines. The neurogenic inflammation also acts to further stimulate the release of CGRP.

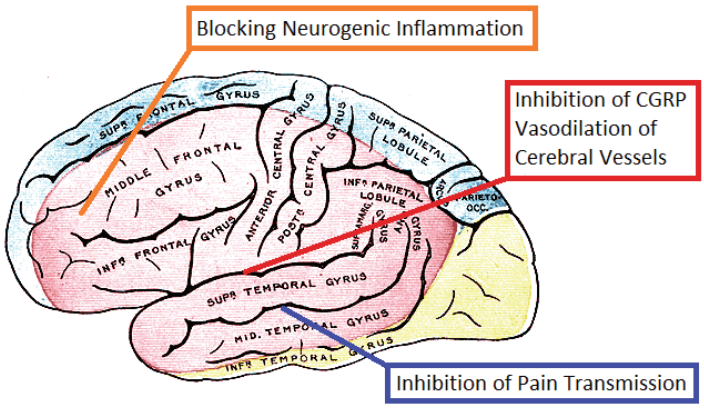
Exhibit 144. Role of Calcitonin Gene-Related Peptide (CGRP) in Migraine



Source: Adapted from Wikipedia, Wells Fargo Securities LLC

The mechanism of CGRP-induction of migraine has also been corroborated by studies where administration of IV CGRP precipitated the onset of migraines. Studies of CGRP antagonism, both direct and indirect, have also confirmed it plays a key role in the pain of migraine. For example, indirect CGRP antagonism has been demonstrated by sumatriptan, which activates (agonist action) serotonin receptors located on trigeminal nerves to inhibit CGRP release. Administration of sumatriptan has been found to decrease CGRP levels in the serum of migraneurs, and subsequently alleviate pain. Direct CGRP antagonism can work at multiple levels to block the action of CGRP, including the ligand, or at multiple receptor sites (see Exhibit 15). Our literature review also found no significant evidence that they have vaso-constrictive activity.

Exhibit 155. Effects of Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists in Migraine



Source: Adapted from Wikipedia, Wells Fargo Securities LLC

Efficacy of small molecule CGRP antagonists supports the mechanistic approach. Targeting the function of CGRP to treat migraine has also been explored in the past by small molecules. Approaches from Merck, Boehringer Ingelheim, and Bristol-Myers Squibb to antagonize CGRP receptor using small molecules have demonstrated improvement in migraine endpoints in clinical trials in the past. These drugs were ultimately limited by issues such as liver toxicity, something we think is likely related to the individual drugs rather than the target.

Clazakizumab

Overview

Clazakizumab is a humanized monoclonal antibody against interleukin-6 (IL-6), an inflammatory cytokine, which has potential as a new treatment in rheumatoid arthritis and psoriatic arthritis. Along with partner Bristol-Myers Squibb, the company is developing injectable Clazakizumab for several autoimmune indications such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA). The companies have completed nine clinical trials to date, including a recent phase IIb in which they demonstrated clear proof-of-concept in RA, and which also suggested potential differentiating attributes from the current market-leading biologics. Clazakizumab is undergoing a final dose-ranging phase IIb RA study prior to expected progression into phase III mid next year. The agent is also in phase II for psoriatic arthritis, with data potentially by year-end.

Prior clinical studies

The most recently conducted phase IIb RA study, in our view, has demonstrated clear, competitive efficacy, which we gives the drug a high likelihood of success in phase III. In this trial (ClinicalTrials.gov identifier: NCT01373151), 418 patients with moderate-to-severe RA who were inadequate responders to methotrexate (MTX) (a standard trial design in this indication) were randomized to placebo in combination with methotrexate (MTX) (group one), Clazakizumab dosing in combination with MTX (groups two to four), Clazakizumab dosing in combination with placebo (groups 5-6), or to Humira in combination with MTX as an active comparator arm (group seven). Regimens in the trial were not adjusted during the initial portion of the trial based upon any ongoing assessment of disease activity, as some other trials in RA biologics have done. The trial ran for six months, with monthly dosing followed by a further six-month extension and open-label extension at a uniform fixed dose. The treatment sequence in Clazakizumab monotherapy (groups 5-6) was initially six months of Clazakizumab in combination with placebo, followed by methotrexate after week 24. The outcomes of response and remission rates in signs and symptoms of RA seen in the trial, as measured by common registrational endpoints of American College of Rheumatology (ACR) scores (primary endpoint ACR20), were presented at the 2013 ACR meeting and are depicted in Exhibit 16.

Exhibit 166. Clazakizumab demonstrated comparable or better efficacy than Humira, and superiority to placebo, in recent phase IIb RA study, with no clear dose dependence

			Response Rates (%)			Remission Rates (%)	
Group	Treatment Arm	Patients	ACR20	ACR50	ACR70	DAS28-CRP < 2.6	CDAI £ 2.8
1	Placebo + MTX	61	39.3	18	6.6	13.1	1.6
2	Claza 25mg + MTX	59	83.1	47.5	27.1	49.2	15.3
3	Claza 100mg + MTX	60	63.3	45	38.3	41.7	20
4	Claza 200mg + MTX	60	66.7	43.3	30	41.7	20
5	Claza 100mg + placebo	60	58.3	36.7	16.7	28.3	6.7
6	Claza 200mg + placebo	59	57.6	33.9	25.4	35.6	6.8
7	Humira + MTX	59	67.8	49.2	18.6	23.7	8.5

Source: Weinblatt M et all, ACR 2013; and Wells Fargo Securities, LLC

The results showed that after six months of treatment, Clazakizumab demonstrated activity, either alone, or in combination with MTX, across all tested dose levels that was greater than that of placebo alone, and in some cases, exceeded that of Humira with MTX. Treatment with Clazakizumab showed higher ACR 20/50/70 response rates, DAS28-CRP and CDAI scores compared to MTX alone after six months. In particular, treatment with Clazakizumab + MTX at all three tested dose levels (25mg/100mg/200mg) saw better improvements in response rates (ACR), and lower disease activity/higher remissions (DAS28-CRP, and CDAI) versus Humira + MTX (a widely used biologic standard of care) after six months. The Clazakizumab monotherapy arms also performed respectably, in our view, well exceeding placebo response rates and remissions, though efficacy generally looked somewhat less robust than that of the MTX combo arms (or the Humira + MTX arm). As such, we see less of a compelling case for use of the drug as monotherapy, though it could be an option for people with very poor tolerability to MTX. Though activity across all Clazakizumab arms was impressive and at least as good as for the marketed biologics, in our view, somewhat oddly, there did not appear to be any evidence of dose dependence; the 25mg dose actually had the highest ACR20 and DAS-28 remission scores. Though this can potentially be explainable by the sample size and may just be noise, we believe it is worth exploring further in the ongoing study to better understand the lowest effective dose. (We do not believe there is any biological rationale as to why the lower dose would have better efficacy).

Potential for differentiation with greater remission achievements

Based on the data from this study, as well as the mechanism, we believe Clazakizumab has some potential elements that could help differentiate it from many other biologics in RA on efficacy. To understand how the data may be suggestive of an efficacy advantage over other biologics, we believe it is important to understand the nuances between several of the tools used in the study for the evaluation of RA disease activity; ACR scores, DAS28, and CDAI criteria:

- **ACR criteria measures response.** ACR scores are a composite of patients' tender and swollen joints and disease activity; with a reduction in the score by 20% a patient is considered to have met the ACR20 endpoint, and so on. While the ACR20/50/70 criteria are well used in clinical trials as a common standard between clinical researchers, and ACR20 is an acceptable regulatory endpoint, ACR scores may be becoming less useful in clinical practice, where clinicians care most about the proportions of patients in whom low disease activity is achieved.

- **ACR70 is becoming a goal.** With vast improvements in RA treatments over the past decade, physicians and patients seek more meaningful disease improvements. The ACR70 score, which represents a 70% improvement in the clinical response criteria, is perhaps the most stringent measurement or profound endpoint of the best outcomes in RA therapy, and is considered evidence of clinically meaningful improvement in the RA disease state.

- **DAS28-CRP and CDAI are other measures of "remission" reflecting an increasing bar for efficacy.** While the ACR scores are a measurement of improvement from a baseline state; in contrast, DAS28 and CDAI are indices that incorporate a set of variables which are measured in the assessment of RA to calculate a continuous score to measure disease activity. The individual variables include counts of swollen and tender joints, acute phase response, a functional evaluation, patient self-assessment of pain, and finally a clinician and patient based global assessment of disease activity, in order to capture the spectrum and variability of the evolution of RA. The variables are pooled into a composite index that provides a single number for improved comparison between patients and across time. CDAI is essentially a slightly simplified version of the DAS28 because it excludes acute phase reactants and has different weighting of common variables though in practice the two demonstrate high correlation. Most important for clinicians, both allow the definition and stratification of patients into categories of low disease activity or remission. While not without flaws, both have been validated in the literature as possessing high sensitivity, specificity, high area under the curve (AUC), and good predictive likelihood ratio, for stratifying the grade of RA disease activity (see Exhibit 17).

Exhibit 177. Interpretation of RA Clinical Scores

	CDAI	DAS28
Remission	CDAI ≤ 2.8	DAS28 < 2.6
Low Disease Activity	2.8 < CDAI ≤ 10	2.6 < DAS28 ≤ 3.2
Moderate Disease Activity	10 < CDAI ≤ 22	3.2 < DAS28 ≤ 5.1
High Disease Activity	CDAI > 22	DAS28 > 5.1

Source: Alder BioPharmaceuticals and Wells Fargo Securities, LLC

Clazakizumab appeared to drive more patients toward optimal benefits than Humira. In the recently completed phase IIb trial, the ACR70s and rates of disease remission seen under treatment with Clazakizumab appeared superior to that of Humira, with 100mg dose levels of Clazakizumab yielding almost twice the proportion of ACR70 improvement as Humira, and 25mg dose levels yielding approximately twice the proportion of patients stratified as in remission (see Exhibit 18).

Exhibit 188. ACR70 and Rates of Disease Remission of Clazakizumab versus Humira in phase IIb

	Response Rate (%)	Remission Rates (%)	
	ACR70 (%)	DAS28-CRP < 2.6	CDAI ≤ 2.8
Placebo + MTX	6.6	13.1	1.6
Clazakizumab 25mg + MTX	27.1	49.2	15.3
Clazakizumab 100mg + MTX	38.3	41.7	20
Clazakizumab 200mg + MTX	30	41.7	20
Humira + MTX	18.6	23.7	8.5

Source: Weinblatt M et all, ACR 2013; and Wells Fargo Securities, LLC

Based on our analysis of historical studies, it did not look like Humira's performance in BMY/Alder's phase IIb differed dramatically from prior experience, though variability in patient populations and endpoints makes it very difficult to know this for sure; however, the fact that such differences in remission rates between Clazakizumab and Humira were observed within the same trial in our view provides comfort that the potential advantages may be real.

Clazakizumab also appears to have remission advantages versus historical studies of other RA biologics such as Actemra and Enbrel (entanercept). Though comparing across trials is difficult, in the six-month, 623-patient phase III OPTION trial of Actemra in RA patients with incomplete response to MTX, Actemra in combination with MTX achieved statistically significant levels of improvement in ACR70 and DAS28 but these did not surpass the rates seen with Clazakizumab. Actemra + MTX achieved ACR70 in 12% and 22% of patients at the 4 mg/kg and 8 mg/kg dose levels, respectively, versus 2% with placebo. DAS28 remission states were achieved in 13% and 27% of the 4mg/kg and 8mg/kg dose levels, respectively versus 0.8% with placebo. In a six-month, 89-patient trial of Enbrel combination therapy with MTX versus MTX, 71%/39% of patients in the active arm achieved ACR20/ACR50, while only 27%/3% in the placebo + MTX arm achieved the same. While the placebo rates were well above those seen in the Clazakizumab phase IIb, the response rates of the active arm were below, suggesting greater improvement in disease activity by Clazakizumab as compared to that historically seen with Enbrel.

There could be a mechanistic explanation from this potentially better activity versus the anti-TNF approach. The biological explanation for the potentially superior efficacy may stem from the incremental effect that IL-6 antagonism has on inhibition of hepcidin production, compared to TNF-α. While the pro-inflammatory cytokines IL-6 and TNF-α share similar effects of inducing and prolonging the systemic inflammation of RA, IL-6 works via the JAK-STAT pathway to stimulate production of acute phase reactants such as hepcidin. Hepcidin protein regulates iron homeostasis, and its inhibition induces the release of iron that has been segregated in macrophages, helping to correct things such as the inflammatory anemia of RA. TNF-α regulates hepcidin expression differently, and does not stimulate production of the protein.

Solid efficacy should make Clazakizumab a competitive entrant

At the least, even if the advantages in optimal responses do not play out in future studies (which might reduce differentiation), the efficacy looks very competitive with other approved biologics, suggesting it should still have a solid place in the treatment paradigm. While we caveat that these data are drawn from individual trials, and not necessarily head-to-head comparisons of the efficacy and safety of different biologic DMARDs, in general placebo-adjusted efficacy for Clazakizumab on ACR scores looks comparable to historical data for other approved anti-TNF and non-anti-TNF biologics at six months when dosed on top of methotrexate (see Exhibit 19).

Exhibit 19. Placebo-adjusted Response and Remissions Rates of RA Biologics in Pivotal Studies

MTX Inadequate Responders at Six Months (Placebo + MTX in parenthesis)		Response Rates (%)			Remission Rates (%)	Other Criteria
		ACR20	ACR50	ACR70	DAS28 < 2.6	EULAR Moderate-to-Good Response
Anti-IL-6	Claza (blended) + MTX	32	27	25	31	
Anti-TNFs	Enbrel + MTX [1]	48	35	14		
	Simponi + MTX [2]	32	23	15	14	
Anti-B-cell	Rituxan + MTX [3]	27	20	10		78
	Rituxan + MTX [4]	33	22	11	9	43
Anti-T-cell	Orencia + MTX [5]	28	23	13		
Anti-IL-6	Actemra 5mg BID + MTX [6]	23			5	
	Actemra 10mg BID + MTX [6]	24			11	
	Actemra 4mg/kg + MTX [a]	24	15	9	15	
	Actemra 8mg/kg + MTX [a]	29	22	11	29	
	Actemra 4mg/kg + MTX [b]	21	21	10		
	Actemra 8mg/kg + MTX [b]	32	33	20		
	Actemra 8mg/kg + MTX [c]	37	29	20		
	Actemra 4mg/kg + MTX [d]	20	13	4		
	Actemra 8mg/kg + MTX [d]	40	25	11		

Notes: 1. Moreland, Larry W., et al. "Etanercept therapy in rheumatoid arthritis: A randomized, controlled trial." Annals of internal medicine 130.6 (1999): 478-486.; 2. GO-FORWARD Trial; 3. Edwards, Jonathan CW, et al. "Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis." New England Journal of Medicine 350.25 (2004): 2572-2581.; 4. REFLEX Trial; 5. AIM (Abatacept in Inadequate Responders to Methotrexate) Trial; 6. van Vollenhoven, R. F. et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N. Engl. J. Med. 367, 508–519 (2012), NCT00853385; a. LITHE (TociLIzumab Safety and THE Prevention of Structural Joint Damage) Trial; b. OPTION (TOcilizumab Pivotal Trial in Methotrexate Inadequate respONders) Trial; c. AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy) Trial; d. RADIATE (RheumAtoiD ArthritIs Study in Anti-TNF FailurEs) Trial
Source: Wells Fargo Securities, LLC

Prior studies of Clazakizumab had also shown definitive benefits consistent with those seen in the phase IIb. In the phase IIa study conducted by Alder using IV administration, Clazakizumab was assessed in moderate to severe RA patients with an inadequate response to MTX in a double-blinded, randomized, placebo-controlled trial lasting four months. A total of 132 patients were initially enrolled and were randomly assigned to placebo in combination with MTX (group one), Clazakizumab 80mg IV, 160mg, or 320mg every two months in combination with MTX (groups two, three, and four). Note that these dose levels were higher than those administered in the phase IIb, but with the 55-60% SC bioavailability, the 320mg approximately equated to the 200mg SC dose given in the phase IIb. Though administration frequency and endpoint time lines differed, we find it reassuring that at the 320mg IV dose, DAS28-CRP remission rates were notably high and in the 40% area, akin to those observed with the highest phase IIb SC dose of Clazakizumab (see Exhibit 20).

Exhibit 190. Response and Remission Rates in Clazakizumab RA phase IIa trial at four months

			Response Rates (%)			Remission Rates (%)
Group	Treatment Arm	Patients	ACR20	ACR50	ACR70	DAS28-CRP < 2.6
1	Placebo + MTX	33	36	15	6	0
2	Claza 80mg IV every two months + MTX	32	75 (p=0.0026)	41 (p=0.028)	22 (p=0.082)	13.8 (p=0.002)
3	Claza 160mg IV every two months + MTX	34	65 (p=0.028)	41 (p=0.029)	18 (p=0.258)	28.1 (p=0.0001)
4	Claza 320mg IV every two months + MTX	28	82 (p=0.005)	50 (p=0.005)	43 (p=0.0015)	44 (p=0.0001)

Source: Alder BioPharmaceuticals S-1, and Wells Fargo Securities, LLC

Safety has looked acceptable, with few surprises

Findings seen in clinical trials to date provide support for the potential long-term safety of Clazakizumab in inflammatory diseases. The safety profile of Clazakizumab at six months in the completed phase IIb demonstrated adverse events (AEs) that were similar in character to those seen historically with Roche's Actemra and generally attributable to the IL-6 mechanism. Rates of AEs and SAEs were higher in phase IIb than in the Humira arm (AEs 83-97% versus 75% for Humira; SAEs9-14%, versus 5% for Humira). As has been seen with Actemra, Clazakizumab increased cholesterol without changing HDL/LDL level, increased hemoglobin, elevated LFTs, and reduced neutrophils and platelets. We believe physicians are accustomed to these side effects given their experience with Actemra and that they are unlikely to be a significant commercial barrier, though we believe they will likely contribute to the anti-TNF drugs likely remaining the initial treatment of choice prior to anti-IL6 medicines. Although not all of these safety parameters have been quantified, a comparison of the safety profile of Clazakizumab monotherapy (to eliminate the effect of MTX on safety markers) compared to that observed for Actemra and Humira in the ADACTA trial reveal a slightly higher rate of low-grade ALT elevations for Clazakizumab, though accompanied by a comparatively lower rate of higher grade ALT elevations. The AE rate is slightly higher on Clazakizumab. BMS has not publicly released data on specific SAEs outside malignancy, though such data may be included in a formal publication of the trial results due later this year. Finally, the rate of infection SAEs appear quite comparable.

Exhibit 201. Clinical Safety Experience across Biologics as Monotherapy in RA

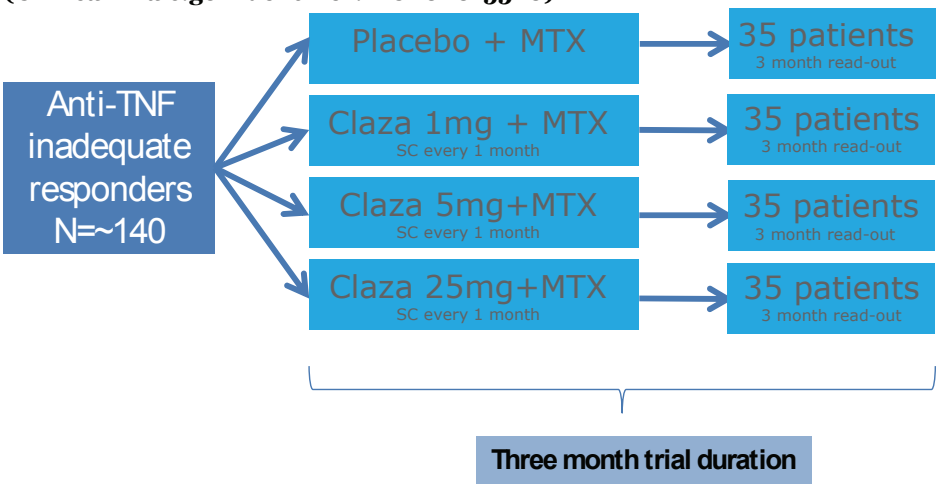
	Clazakizumab phase IIb Montherapy (both arms)	Tocilizumab	Adalimumab
	N = 119	N = 163	N = 162
ALT Elevations			
Grade 1 (>1-3 ULN in Claza, >1-2.5 in Ada/Toc)	40.3%	30.9%	24.7%
Grade 2 (>3-5 ULN in Claza, >2.5-5 in Ada/Toc)	0.8%	5.6%	1.9%
Grade 3 (>5-8 ULN in Claza, >5-20 in Ada/Toc)	0.0%	appx. 1%	appx. 1%
Adverse Effects	104	443	430
Patients with ≥ 1 AE, n (%)	87.4%	83.0%	82.0%
Serious Adverse Effects	13	21	23
Patients with ≥ 1 SAE, n (%)	10.9%	10.0%	12.0%
Myocardial infarction or acute coronary syndrome		1%	1%
Stroke		1%	1%
Cancer/Malignancy	0%	1%	1%
Hypersensitivity Reaction		0%	1%
Infection AEs		106	113
Patients with ≥ 1 infection AE, n (%)		42.0%	48.0%
Infection SAEs	4	7	6
Patients with ≥ 1 infection SAE, n (%)	3.4%	3.0%	3.0%
Deaths, n (%)	0 (0)	0 (0)	2 (1)

Source: "Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomized, double-blind, controlled phase 4 trial," NCT01119859 from ClinicalTrials.gov, "A Phase IIb Study Of The Efficacy and Safety Of Subcutaneous Clazakizumab (anti-IL-6 monoclonal antibody) With Or Without Methotrexate In Adults With Moderate-To-Severe Active Rheumatoid Arthritis and An Inadequate Response To Methotrexate," Presented at the American College of Rheumatology 2013 Meeting, Wells Fargo Securities, LLC

Ongoing and future RA studies

An ongoing phase IIb study will seek to clarify dose responses. The question of whether a dose-response relationship has been characterized satisfactorily is one of the most frequently discussed issues during FDA advisory committee meetings for drugs, and is of importance to the FDA, in particular to ensure that patients receive the lowest effective doses of a drug to reduce theoretical risk of side effects. As previously mentioned, in the recent phase IIb RA study, the 25mg Clazakizumab dose actually appeared to produce more responses than the 200mg dose level, on ACR20 and DAS28. Although these differences are likely not meaningful and do not necessarily suggest, in our view, that there is actually an inverse dose-response relationship, we do not believe it is surprising that FDA asked BMY to conduct an additional study evaluating lower doses prior to initiation of registrational studies, and believe this information will be useful for BMY and Alder to clarify anyway. We would also not be surprised to see FDA requesting an additional six-month or any longer term safety follow-up beyond the 24-week endpoint for measurement to deepen the safety database of '403. As such, BMY is now conducting a placebo-controlled, three month study evaluating the lowest dose from the phase IIb, 25mg, as well as 1mg and 5mg dose levels (see Exhibit 22).

Exhibit 212. Design of ongoing Clazakizumab dose-ranging phase IIb trial in RA (ClinicalTrials.gov identifier: NCT02015520)



Source: Alder BioPharmaceuticals S-1, ClinicalTrials.gov, Wells Fargo Securities, LLC

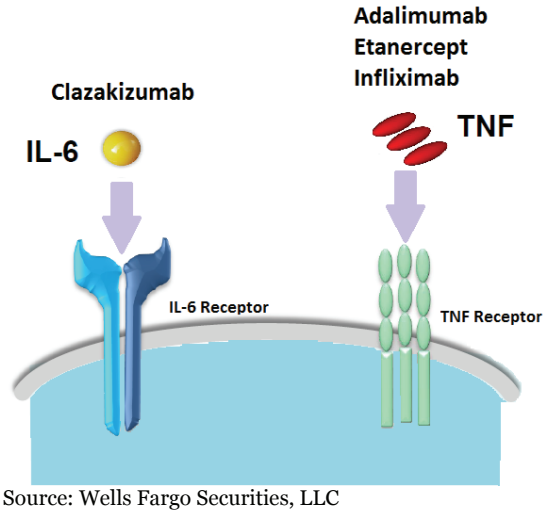
We see minimal downside risk to this ongoing study and believe it will provide beneficial additional information about Clazakizumab's properties. The trial is expected to complete around year-end 2014; data could be top-lined around that time and/or presented at the next rheumatology medical meeting, likely EULAR mid-2015. We see limited risk to the trial demonstrating efficacy, at the higher 25mg dose that already showed strong activity in the first phase IIb study; even if the efficacy looks less robust than what was previously observed, we believe BMY is still highly committed to proceeding into phase III with the program (and would just use the higher doses for phase III). We note that this is a more refractory population than in the phase IIb, as they are inadequate responders to anti-TNFs, so responses are likely to look less robust across the board. On the positive side, while results may not provide a major catalyst for shares since the proof-of-concept is already established, results and progression into phase III could help the company generate more attention from investors. If the lower doses also show comparable response and remission rates with an even cleaner safety profile, this could also potentially further the case for differentiation commercially; we note that in the phase IIb, the lowest 25mg dose when combined with MTX had the lowest rate of ALT elevations >3x ULN, though reported lipid changes, infections, and AST elevations did not appear to show meaningful dose dependence, so ALT may be one area lower doses could potentially look even better on in the ongoing study.

We believe phase IIIs for Clazakizumab in RA will likely involve head-to-head studies with other biologic(s) as activate comparator(s), in an effort to maximally differentiate the drug's profile. Given the signals of efficacy advantages vs. currently-used biologics such as Humira, our sense is that BMY may structure their phase III program to include head-to-head studies against Humira potentially with a superiority component, in an effort to position the drug more as a "first-line" option for DMARD failures. Though our feedback from physicians suggests it would be difficult to displace highly entrenched therapies Humira and Enbrel from their place as the initial biologics of choice, such a phase III trial design should at least highlight potential any differentiating advantages, and perhaps make a better case for the drug to be used as the next-in-line biologic, still a robust market opportunity, in our view. Based on typical FDA requirements

for phase III studies, we believe the phase III program would likely consist of at least three trials enrolling about 3,000 patients in total. With drug supply and toxicology studies ready to go, we expect a phase III program could commence shortly after the ongoing dose-ranging study is complete, by mid-2015; based on historical time lines for phase III enrollment, we believe the first data could be available around mid-201 7.

In addition to the clear phase IIb data, the validation of the IL-6 target biologically and clinically we believe gives the phase III program a high probability of success. IL-6 is an inflammatory mediator known to play key role in autoimmune diseases like RA. Roche's Actemra, a successfully marketed RA drug works by inhibiting the IL-6 receptor. While Clazakizumab inhibits the endogenous IL-6 ligand itself, rather than the receptor, we believe Actemra still provides proof of principle for the general approach of IL-6 inhibition, which, along with the generated clinical data to date, reduces the risk, in our view, that an unexpected efficacy or safety issue emerges in the phase III. Additionally, we note there are some theoretical benefits that targeting the ligand could have, including theoretically less risk of neutropenia. While numerous cell types produce IL-6, IL-6 receptor is the only known receptor for IL-6, and it is expressed primarily by hepatocytes and immune cells such as neutrophils.

Exhibit 223. Differentiated IL-6 Mechanism of Action of Clazakizumab



Source: Wells Fargo Securities, LLC

Competitive landscape and crowded market are important considerations

The largest risk, in our view, is the crowded commercial and development space, which creates a high barrier, both regulatory and with respect to commercialization and adoption, for new entrants. There are currently ten biologic drugs approved for RA, including TNF inhibitors, anti-CD80/anti-T-cell, anti-CD20/anti-B-cell, IL-1 receptor blocking antibody, and an IL-6 receptor blocking antibody, Roche's Actemra. These drugs are typically used after failure of methotrexate or other DMARDs, and have been well entrenched for years, with rheumatologists highly accustomed to their profiles. Most of these drugs offer once every 1-4 week subcutaneous dosing profiles, acceptably convenient for most patients. For patients unwilling to self-inject, Pfizer's Jak inhibitor Xeljanz offers a comparably efficacious alternative, and Lilly/Incyte's baricitinib could provide another oral alternative. As Actemra is the only currently-marketed antibody against the IL-6 pathway, we believe it will be particularly important for Clazakizumab to show differentiation from this drug.

There are also several other IL-6 targeted drugs in mid- to late-stage clinical development, including at least one antibody that like Clazakizumab targets the ligand. IL-6 biologics in development, their stage, and some of the clinical data generated to date are depicted below; we view JNJ/GSK's sirukumab as the most important direct competitor, as it also targets the IL-6 ligand and is about 1-2 years ahead (see Exhibit 24):

Exhibit 234. Other biologics targeting IL-6 in mid- to late-stage development for RA

Drug	Sponsor	IL-6 target	Data to date	Trial status	Comments
Sirukumab	JNJ/GSK	Ligand	In ph.II study on top of MTX, 100mg SC every 2wks produced 75% ACR20 and 38% "good" DAS-CRP scores	Ph.IIIs including in DMARD and TNF failures initiated Aug 2012; HTH study vs. Humira in MTX-failures also ongoing; 100mg every 2wks and 50mg every month being tested	Most comparable competitor to Clazakizumab, and 1-2 years ahead in development Shorter half-life (14d) and 50mg qmonthly did not look as robust in ph.II, suggesting Clazakizumab could retain dosing advantage
Sarilumab	SNY/REGN	Receptor	Ph.IIb showed ACR20 58-66%, ACR70 20-25%, on top of MTX	Ph.IIIs vs. Actemra and Enbrel and in TNF failures initiated late-2012/early-2013.	Pivotal program more focued on TNF non-responders Dosing every 1-2 weeks less optimal than Clazakizumab's monthly dosing profile
Olokizumab	UCB/R-Pharm	Ligand	Ph.IIb showed significant improvements in disease activity scores but insufficient differentiation vs. active Actemra arm	Out-licensed to R-Pharm in 2013; future development status unclear	-
ALX-0061	Ablynx/AB BV	Receptor (nanobody)	In ph.I/II study on top of MTX showed ACR20 of 68%, ACR70 of 25%, DAS remission 50%, with some responses with q8wk regimen	Ph.I IV/SC bioavailability study recently initiated	Promising data with potentially long half-life though much earlier in development

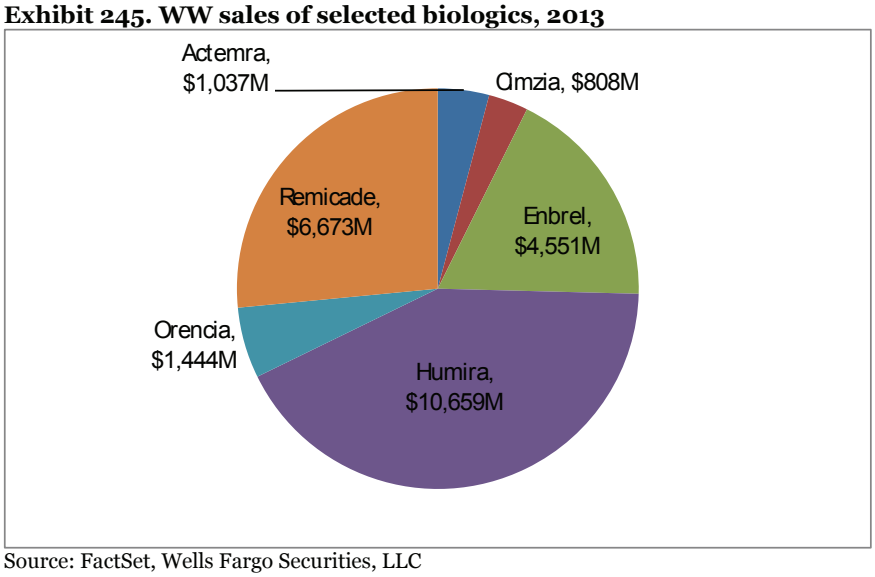
Source: BioMedTracker, Wells Fargo Securities, LLC

Despite the crowded competitive landscape, we believe Clazakizumab could have several potential advantages to draw from that could help enable it to stand out and gain adoption if approved. These include the high potency and induction of remissions (discussed previously), a longer half-life enabling effectiveness with monthly dosing (improving patient convenience), theoretically greater pricing flexibility particularly if 25-100mg monthly dosing is successful and given Alder's manufacturing technology's intrinsic cost of goods sold (COGS) advantage, and better injection tolerability given that the antibody is aglycosylated. While many of these may play out as more incremental advantages, over time and with greater clinician experience, they could add up to a profile of a best-in-class non-TNF biologic.

Market Opportunity

The RA market is very large, with multiple blockbuster biologics. Rheumatoid arthritis is one of the most highly prevalent autoimmune disorders, with approximately 2-2.4 million Americans and approximately 5 million Europeans (based on disease prevalence rate of 1% in Caucasians) suffering from the disease. The large addressable market in RA, where patients are started on disease-modifying anti-rheumatic drug (DMARD) therapy, biologic or otherwise, early in their course of treatment, should allow Clazakizumab to see early commercial opportunity. We list for comparison sales of several selected biologics; though we note some of these are used extensively outside of RA, we believe this provides a sense for the size of the overall market for similar types of therapies (see Exhibit 25).

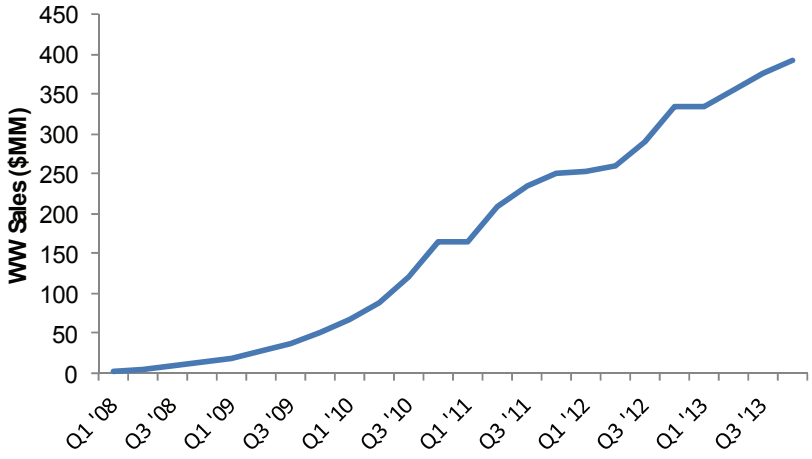
Exhibit 245. WW sales of selected biologics, 2013



Source: FactSet, Wells Fargo Securities, LLC

Though the space is crowded, we believe there is ample evidence for acceptance of new biologics over time. Our discussions with clinicians has suggested it takes some time to get accustomed to efficacy and safety profiles of new biologics in RA, but that this tends to occur over time. For instance, with Actemra, particularly relevant given the mechanistic similarity to Clazakizumab, physicians were initially concerned about bowel perforations, as well as the neutropenia and lipid changes discussed previously. As such, that agent was initially relegated to later lines of treatment. However, as physician experience with the drug grew, physician feedback suggests that more community doctors embraced it and that it moved into earlier lines of treatment, likely mirrored in the steady growth of the drug since the initial launch (see Exhibit 26).

Exhibit 256. Quarterly sales of Roche's Actemra since launch indicate increasing physician acceptance of new biologics as experience grows, and demonstrating growing comfort with IL-6 mechanism



Source: FactSet, Wells Fargo Securities, LLC

The physician experience and comfort with the IL-6 mechanism could enable Clazakizumab to have more rapid traction compared to Actemra at its launch, though BMY/Alder also plans to launch into a more crowded space versus when Roche launched Actemra. Additionally, we would still expect an IL-6 therapy, given its side effects, to occupy a later line of treatment as compared to anti-TNFs.

We believe Clazakizumab could be launched in 2018 and have worldwide sales of $1.1B in RA by 2023, generating $187M in potential royalties for Alder.

Exhibit 7. Revenue build for Clazakizumab in RA

		2018	2019	2020	2021	2022	2023
United States	Overall population	328,857,000	331,375,000	333,896,000	336,416,000	338,930,000	341,436,000
	RA incidence	95,369	96,099	96,830	97,561	98,290	99,016
	RA prevalence pool	2,753,519	2,848,888	2,944,987	3,041,817	3,139,377	3,237,667
	Moderate-severe disease (%)	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%
	Number with moderate-severe disease	1,652,112	1,709,333	1,766,992	1,825,090	1,883,626	1,942,600
	1st-line treatment rate (%)	30.0%	30.0%	30.0%	30.0%	30.0%	30.0%
	1st-line number of moderate-severe patients treated	495,633	512,800	530,098	547,527	565,088	582,780
	MTX monotherapy treatment (%)	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
	Combination DMARD therapy (%)	20.0%	20.0%	20.0%	20.0%	20.0%	20.0%
	Combination DMARD therapy number treated	99,127	102,560	106,020	109,505	113,018	116,556
	Clazakizumab penetration (%)	*0.5%*	*1.1%*	*1.7%*	*2.3%*	*2.9%*	*3.5%*
	1st-line Clazakizumab treatments	496	1,128	1,802	2,519	3,278	4,079
	2nd-line treatment rate (initial DMARD failures) (%)	40.0%	40.0%	40.0%	40.0%	40.0%	40.0%
	2nd-line number treated	198,253	205,120	212,039	219,011	226,035	233,112
	Add/switch biologic (anti-TNF and non-TNF) (%)	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
	Add/switch number treated	99,127	102,560	106,020	109,505	113,018	116,556
	Clazakizumab penetration (%)	*0.7%*	*2.0%*	*3.3%*	*4.6%*	*5.9%*	*7.2%*
	2nd-line Clazakizumab treatments	694	2,051	3,499	5,037	6,668	8,392
	3rd-line treatment rate (%)	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%
	3rd-line number treated	118,952	123,072	127,223	131,406	135,621	139,867
	Add/switch biologic (anti-TNF and non-TNF) (%)	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
	Add/switch number treated	59,476	61,536	63,612	65,703	67,811	69,934
	Clazakizumab penetration (%)	*2.0%*	*4.0%*	*6.0%*	*8.0%*	*10.0%*	*12.0%*
	3rd-line Clazakizumab treatments	1,190	2,461	3,817	5,256	6,781	8,392
	Number of pts on Clazakizumab	2,379	5,641	9,118	12,812	16,727	20,864
	Price	$33,765	$34,778	$35,822	$36,896	$38,003	$39,143
	Compliance	85%	85%	85%	85%	85%	85%
	U.S. Clazakizumab sales	**$68,279,599**	**$166,750,390**	**$277,618,124**	**$401,811,285**	**$540,313,338**	**$694,165,291**
Europe	Overall population	511,913,288	513,139,488	514,365,687	515,314,370	516,263,053	517,211,737
	RA incidence	148,455	148,810	149,166	149,441	149,716	149,991
	RA prevalence pool	4,372,943	4,521,398	4,670,209	4,819,375	4,968,816	5,118,532
	Moderate-severe disease (%)	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
	Number with moderate-severe disease	2,186,472	2,260,699	2,335,104	2,409,687	2,484,408	2,559,266
	1st-line treatment rate (%)	30.0%	30.0%	30.0%	30.0%	30.0%	30.0%
	1st-line number of moderate-severe patients treated	655,941	678,210	700,531	722,906	745,322	767,780
	MTX monotherapy treatment (%)	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
	Combination DMARD therapy (%)	20.0%	20.0%	20.0%	20.0%	20.0%	20.0%
	Combination DMARD therapy number treated	131,188	135,642	140,106	144,581	149,064	153,556
	Clazakizumab penetration (%)	*0.0%*	*0.5%*	*1.1%*	*1.7%*	*2.3%*	*2.9%*
	1st-line Clazakizumab treatments	0	678	1,541	2,458	3,428	4,453
	2nd-line treatment rate (initial DMARD failures) (%)	40.0%	40.0%	40.0%	40.0%	40.0%	40.0%
	2nd-line number treated	262,377	271,284	280,213	289,162	298,129	307,112
	Add/switch biologic (anti-TNF and non-TNF) (%)	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
	Add/switch number treated	131,188	135,642	140,106	144,581	149,064	153,556
	Clazakizumab penetration (%)	*0.0%*	*0.7%*	*2.0%*	*3.3%*	*4.6%*	*5.9%*
	2nd-line Clazakizumab treatments	0	949	2,802	4,771	6,857	9,060
	3rd-line treatment rate (%)	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%
	3rd-line number treated	157,426	162,770	168,128	173,497	178,877	184,267
	Add/switch biologic (anti-TNF and non-TNF) (%)	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
	Add/switch number treated	78,713	81,385	84,064	86,749	89,439	92,134
	Clazakizumab penetration (%)	*0.0%*	*2.0%*	*4.0%*	*6.0%*	*8.0%*	*10.0%*
	3rd-line Clazakizumab treatments	0	1,628	3,363	5,205	7,155	9,213
	Number of pts on Clazakizumab	0	3,255	7,706	12,434	17,441	22,726
	Price	$20,580	$20,374	$20,170	$19,969	$19,769	$19,571
	Compliance	85%	85%	85%	85%	85%	85%
	EU Clazakizumab sales	**$0**	**$56,377,474**	**$132,116,112**	**$211,047,955**	**$293,066,356**	**$378,067,674**
	Clazakizumabin RA WW sales	**$68,279,599**	**$223,127,864**	**$409,734,236**	**$612,859,241**	**$833,379,694**	**$1,072,232,965**
	ALDR Royalties from Clazakizumab RA WW sales	**$10,241,940**	**$33,469,180**	**$65,557,478**	**$101,121,775**	**$141,674,548**	**$187,640,769**

Source: Wells Fargo Securities, LLC estimates

The drug is also being tested in psoriatic arthritis in a phase II, which we believe could add about $80M in royalties in 2023. In PsA, biologic DMARDs are typically used after the failure of non-steroidal anti-inflammatory drugs (NSAIDs) and inadequate response to a second-line non-biologic DMARD (i.e., MTX). However, because there is a lack of evidence proving DMARDs slow or prevent musculoskeletal damage seen in radiology, biologics are gaining prominence in the paradigm of clinical practice, when patients do not respond to NSAIDs and are affected by aggressive disease with radiological signs of structural damage. Based on the phase II, which is to read-out year-end 2014, BMS is positioning Clazakizumab as "third-line" treatment, after patients have failed NSAIDs and non-biologic disease-modifying anti-rheumatic drugs, or DMARDs. Current biologics approved for PsA include Humira, Enbrel, Remicade, and Simponi, and we believe with data showing comparative efficacy, the potentially monthly SC dosing profile of Clazakizumab could provide a competitive dosing profile. While the effectiveness of the currently marketed IL-6 therapy for RA, Actemra, has not yet been fully explored in psoriatic arthritis, IL-6 has a significant role in the pathogenesis of PsA, and case reports in the literature provide efficacy data points for that IL-6 modulator, suggesting a reasonable probability of success for Clazakizumab in PsA.

Bristol-Myers partnership provides validation and a strong development/commercial collaborator

We believe having BMY as a partner provides Alder with an experienced drug development and commercial collaborator, and full funding for a potentially expensive pivotal program. In the collaboration with BMY, established in November 2009, Alder received $85 million upfront. Since that time, the company has received an additional $19 million in milestones, as well as $27 million for clinical supply development costs (through end-2013). Under the terms of the agreement, Bristol pays 100% of development costs in indications outside of cancer, meaning BMY is to pay for the full extent of the registrational program in RA (similar programs have cost upwards of $500 million to conduct). Alder retains full rights to the drug in cancer indications, with BMY entitled to a co-development option with potential commercial rights ex-U.S.; though cancer is deprioritized, we believe it could still be an interesting indication long-term given recent data suggestive of benefits in solid tumors for drugs that target the inflammatory cascade. Alder receives mid-teens to 20% royalties on Clazakizumab sales from Bristol-Myers Squibb.

We believe the potential milestones ALDR could receive provide a high-probability source of non-dilutive financing likely to be underappreciated, in our view, particularly given the relatively low risk we foresee to the drug making it over the finish line. Under the collaboration, Alder is entitled to receive a total of $1.35 billion in milestones. Notably, the company stands to receive an additional $394 million in development and regulatory milestones in RA, alone. Given our view that Clazakizumab is highly likely to succeed in phase III, we believe these milestones are relatively low risk for Alder, and should provide a key source of non-dilutive financing over the next several years. Alder is also eligible to receive an additional $500 million in commercial milestones in the RA indication.

Biologics Manufacturing Platform

Alder has a differentiated platform for the discovery and efficient production of antibodies. The company's proprietary protein manufacturing platform utilizes a differentiated yeast-based system which takes advantage of scalability and versatility, similar to that of bacteria-based manufacturing systems, yet maintaining vital characteristics of a eukaryotic manufacturing system. We believe the most differentiated aspect of Alder's antibody platform is their manufacturing technology using the yeast strain, *Pinchia pastoris*, which allows rapid selection and optimization of cell lines for manufacturing, scalability, and lower susceptibility to viral contamination. In addition, the *Pinchia* yeast system is optimal for manufacturing multimeric and complex proteins by virtue of a system which allows characterization of each subunit of the multimeric complex in different strains (haploids) and subsequently combined (diploid) to effectively produce individually optimized proteins into a wholly assembled protein. While the company has been primarily focused on therapeutic antibodies, other proteins (e.g., cytokines and growth factors) were efficiently manufactured using the system.

There are two main components to ALDR's technology, involving antibody selection (ABS) and manufacturing (MabXpress):

- **ABS antibody discovery and selection system.** The company's target antibody discovery and selection process uses high-throughput screening system to identify the most therapeutically relevant antibodies. For the most part, the company's antibody discovery approach follows the general principles similar to conventional antibody discovery processes: (1) A target protein of interest is immunized in rabbits and the ensuing B cell population is isolated and interrogated for binding and biological activity using ALDR's proprietary system (versus traditional hybridoma generation and screening), (2) Once the B cell clone(s) is isolated, the monoclonal is characterized and validated, (3) A lead candidate antibody gene is isolated and undergoes "humanization" and further optimization through genetic engineering. Notably, rabbit antibody gene is more similar to that of humans (vs. mouse) such that only minimal changes are required for the humanization process, and therefore, lessening the chance of genetic modification that might compromise antibody function.

- **MabXpress.** Once the lead candidate antibody is identified, the corresponding gene is cloned (transferred) into the company's yeast manufacturing system. Antibody structure consists of two chains corresponding to two separate "genes," the light chain and heavy chain. When expressed together, they assemble into a fully functional antibody. The haploid/diploid system, unique to the yeast system, allows individualized optimization of each subunit of the antibody for maximal stability and yield.

  There are several advantages of the MabXpress manufacturing compared with the more traditional CHO-cell based system, illustrated below, which in the end, we believe enable Alder capabilities to rapidly and inexpensively produce antibodies at very large scales, ultimately reducing production and manufacturing costs and potentially enabling the company to develop biologic drugs in lower priced spaces where COGS might have previously been prohibitive (see Exhibit 28).

Exhibit 268. Comparison of MabXpress with CHO

Characteristics	MabXpress	CHO
Cell line selection	Upto 1 month	6-9 months
Fermentation cycle time	5-7 days	15-30 days
Maximum scale	Up to 160,000 L	Up to 25,000 L
Viral contamination QA	Not applicable	3-6 months

Source: Company reports and Wells Fargo Securities, LLC

Intellectual Property

We believe Alder has solid IP protection around their two lead programs, Clazakizumab and ALD403, comprised of both composition of matter, method of manufacturing, and method of treating various conditions using the agents. IP around Clazakizumab is most mature and extensive. The main composition of matter patent is '340, expiring in 2028, which protects the specific protein moiety specified by the nucleic acid sequences of various antibody chains. In addition, there are numerous issued patents and application that contemplates method of treating various inflammation-related conditions, which could extend IP protection until 2032. ALD403 IP portfolio appears to be quite extensive as well though the filings were done relatively recently (2012). ALD403 patent applications include composition of matter as well as several method of treatment claims mainly directed at conditions related to migraine. The company also has several issued patents and applications around their proprietary *Pinchia* yeast-based manufacturing technology.

Exhibit 29. Patent and applications on ALDR's key products and MabXpress manufacturing platform

Number	Title	Type	Est. Expiration
Clazakizumab			
US 7,935,340	Antibodies to IL-6 and use thereof	composition	2028
US 7,906,117	Antagonists of IL-6 to prevent or treat cachexia, weakness, fatigue, and/or fever	method	2028
US 8,062,864	Nucleic acids encoding antibodies to IL-6, and recombinant production of anti-IL-6 antibodies	composition and method	2029
US 8,535,671	Methods of reducing CRP and/or increasing serum albumin in patients in need using IL-6 antibodies of defined epitopic specificity	method	2031
US 8,252,286	Antagonists of IL-6 to prevent or treat thrombosis	method	2032
US 8,277,804	Antagonists of IL-6 to prevent or treat thrombosis	method	2029
US 8,323,649	Antibodies to IL-6 and use thereof	method	2029
ALD403			
WO2012162243A2	ANTI-CGRP COMPOSITIONS AND USE THEREOF	composition	2032
WO2013162257A3	USE OF ANTI-CGRP ANTIBODIES AND ANTIBODY FRAGMENTS TO PREVENT OR INHIBIT PHOTOPHOBIA OR LIGHT AVERSION IN SUBJECTS IN NEED THEREOF, ESPECIALLY MIGRAINE SUFFERERS	method	2032
WO2012162253A2	USE OF ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES OR ANTIBODY FRAGMENTS TO TREAT OR PREVENT CHRONIC AND ACUTE FORMS OF DIARRHEA	method	2032
MabXpress			
US8268582	Methods of synthesizing heteromultimeric polypeptides in yeast using a haploid mating strategy	method	2024
US7927863	Methods of synthesizing heteromultimeric polypeptides in yeast using a haploid mating strategy	method	2026

Source: USPTO, WTO, and Wells Fargo Securities, LLC

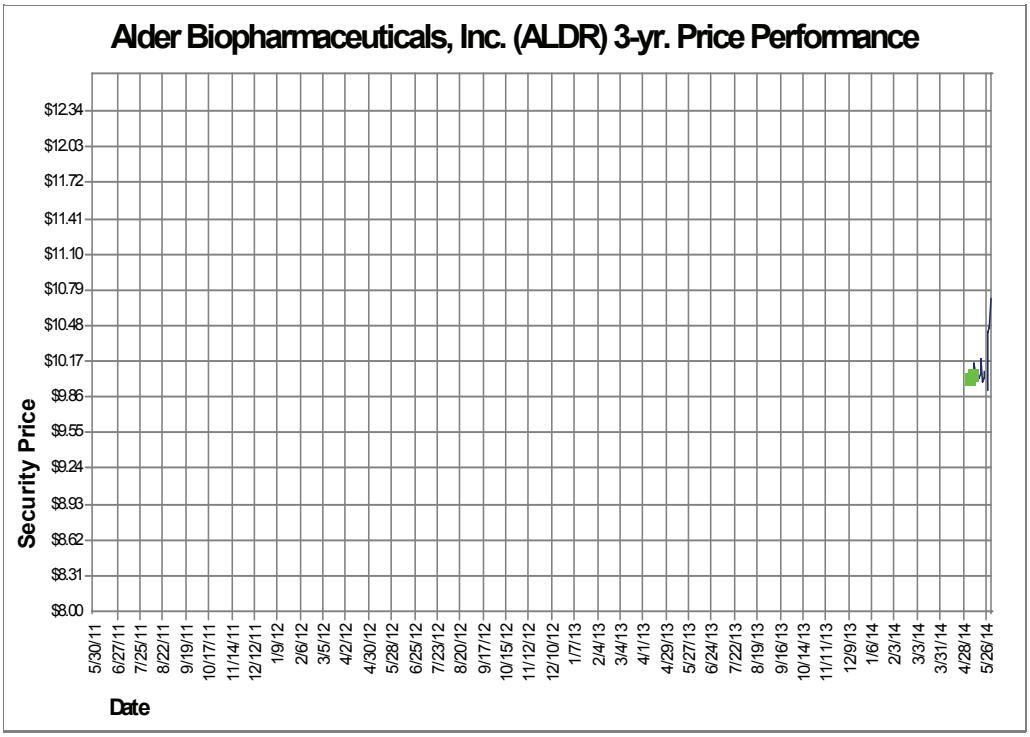
Income Statement

Alder Biopharmaceuticals (ALDR)
Statement of Operations

	2012A	2013A	1QE	2QE	3QE	4QE	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E
Revenues																
Clazakizumab sales											*$68,280*	*$321,087*	*$604,979*	*$886,793*	*$1,195,036*	*$1,525,578*
ALD403 sales												*97,549*	*311,435*	*641,157*	*1,027,741*	*1,448,953*
Clazakizumab royalties	-	-	-	-	-	-	-	-	-	-	10,242	48,163	96,797	146,321	203,156	266,976
ALD403 U.S. sales	-	-	-	-	-	-	-	-	-	-	-	91,549	264,479	505,197	767,467	1,052,724
ALD403 Ex-U.S. royalties	-	-	-	-	-	-	-	-	-	-	-	-	7,982	23,113	44,247	67,359
Collaborative and license agreements/revenue (1)	20,067	18,796	4,800	4,036	4,036	4,036	16,907	51,143	34,714	84,714	184,714	92,571	87,571	37,571	72,571	79,000
Total revenues, net	**$20,067**	**$18,796**	**$4,800**	**$4,036**	**$4,036**	**$4,036**	**$16,907**	**$51,143**	**$34,714**	**$84,714**	**$194,956**	**$232,284**	**$456,830**	**$712,202**	**$1,087,441**	**$1,466,059**
Expenses																
Cost of goods sold												$6,408	$18,514	$35,364	$53,723	$73,691
Research and development	$30,669	$31,883	$7,800	$8,200	$8,500	$9,000	$33,500	$45,225	$62,411	$78,013	$93,616	$97,360	$92,492	$87,868	$91,382	$95,038
Selling, general and administrative	$7,217	$7,674	$2,400	$2,600	$2,650	$2,700	$10,350	$11,385	$12,524	$17,533	$52,599	$78,898	$102,567	$123,081	$128,004	$133,124
Total operating expenses	**$37,886**	**$39,557**	**$10,200**	**$10,800**	**$11,150**	**$11,700**	**$43,850**	**$56,610**	**$74,934**	**$95,546**	**$146,214**	**$182,667**	**$213,573**	**$246,312**	**$273,109**	**$301,853**
Operating Income	**($17,819)**	**($20,761)**	**($5,400)**	**($6,764)**	**($7,114)**	**($7,664)**	**($26,943)**	**($5,467)**	**($40,220)**	**($10,832)**	**$48,742**	**$49,617**	**$243,256**	**$465,890**	**$814,332**	**$1,164,206**
Interest income	$101	$54	$9	$23	$36	$31	$99	$166	$278	$296	$273	$323	$579	$1,253	$2,500	$4,467
Other income	-	158	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Interest expense	(88)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other expense	-	(64)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total other income	**$13**	**$148**	**$9**	**$23**	**$36**	**$31**	**$99**	**$166**	**$278**	**$296**	**$273**	**$323**	**$579**	**$1,253**	**$2,500**	**$4,467**
Income before taxes	**($17,806)**	**($20,613)**	**($5,391)**	**($6,742)**	**($7,078)**	**($7,633)**	**($26,844)**	**($5,301)**	**($39,942)**	**($10,536)**	**$49,015**	**$49,939**	**$243,836**	**$467,143**	**$816,832**	**$1,168,673**
Income tax (expenses)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	($980)	($1,998)	($24,384)	($79,414)	($179,703)	($303,855)
Net income	($17,806)	($20,613)	($5,391)	($6,742)	($7,078)	($7,633)	($26,844)	($5,301)	($39,942)	($10,536)	$48,035	$47,942	$219,452	$387,729	$637,129	$864,818
Earnings Per Share	**($19.54)**	**($0.94)**	**($0.25)**	**($0.26)**	**($0.24)**	**($0.25)**	**($1.00)**	**($0.15)**	**($1.10)**	**($0.29)**	**$1.09**	**$1.07**	**$4.84**	**$8.44**	**$13.69**	**$18.35**
Shares Outstanding (Basic)	911	21,889	21,889	25,900	29,900	30,050	26,935	35,650	36,250	36,850	37,450	38,050	38,650	39,250	39,850	40,450
Shares Outstanding (Diluted)			28,578	32,589	36,589	36,739	33,623	42,339	42,939	43,539	44,139	44,739	45,339	45,939	46,539	47,139

Source: Company reports and Wells Fargo Securities, LLC estimates
Note: In 000's $, except per share amounts; Fiscal year ends December 31
(1) includes milestone payments and amortization of upfront payments

Required Disclosures



	Date	Publication Price ($)	Rating Code	Val. Rng. Low	Val. Rng. High	Close Price ($)
❐	5/8/2014		IPO at $10.00			

Source: Wells Fargo Securities, LLC estimates and Reuters data

Symbol Key

- ▼ Rating Downgrade
- ▲ Rating Upgrade
- ● Valuation Range Change
- ◆ Initiation, Resumption, Drop or Suspend
- ■ Analyst Change
- ❐ Split Adjustment

Rating Code Key

1	Outperform/Buy	SR	Suspended
2	Market Perform/Hold	NR	Not Rated
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ALDR: Risks include emergence of a safety signal, and competition in the migraine/RA spaces.

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