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Achaogen, Inc. (AKAO - $15.40 - NASDAQ) — Initiation - Hold

Year	EPS [a]	PMV	
2016P	($1.00)	$19	Dividend: None Current Return: Nil
2015P	(1.20)	19	Shares O/S: 17.7 million
2014E	(1.60)	18	52-Week Range: $19.69 – $11.66
2013A	--	--	

(a) Excludes EPS prior to IPO in 2014

COMPANY OVERVIEW

Achaogen, headquartered in South San Francisco, CA, is a clinical stage pharmaceutical with plazomicin, a novel aminoglycoside antibiotic, in Phase III for the treatment of carbapenem-resistant *Enterobacteriaceae* (CRE) infections. The company went public in March 2014 at an IPO price of $12 per share.

- Plazomicin is being developed to specifically target CRE, a Gram-negative class of bacteria that is heavily resistant to many existing antibiotics. The CDC classifies CRE as an urgent threat to public health and estimates that at least 9,300 hospital patients in the US are infected with CRE annually, resulting in over 600 deaths. Achaogen estimates that the addressable market for CRE bloodstream and pneumonia infections in the US and major EU countries is approximately 30,000 patients annually.

- The single 360-patient open-label Phase III study is being conducted under a Special Protocol Agreement (SPA) with the FDA. Unlike most other antibiotic studies, the Phase III for plazomicin will seek to demonstrate superiority to an active comparator (Colistin) with a primary endpoint of reduced mortality. Given the lack of options for CRE and the opportunity to demonstrate superiority to current standard of care, Achaogen believes that plazomicin could have premium pricing around $15,000/course of therapy (4-5x current branded pricing). Top-line data are expected in 2017 with potential FDA approval in 2018. The company estimates that it has enough cash to get to the top-line data readout but would need additional funding to support a drug launch.

- A Phase II study demonstrated non-inferiority in cUTI for plazomicin, but the drug has not demonstrated proof of concept clinically for CRE, reduced mortality, or safety for dosing beyond five days (Phase III is 7-14 days). The drug has shown a side effect profile consistent with aminoglycosides (kidney and inner ear toxicity) along with signs of hypotension.

- We are initiating coverage of Achaogen with a Hold recommendation. We believe that the current stock price does not provide an adequate margin of safety given the risks associated with the Phase III program (no clinical proof-of-concept, slow enrollment), premium pricing model, and potential Gram-negative market entrants prior to 2018. AKAO shares currently trade at a 19% discount to our 2015 PMV of $19 per share.

Table 1

Achaogen, Inc.
Income Statement
2012A – 2020P

($ in millions except per share)

FYE 12/31	2012A	2013A	2014E	2015P	2016P	2017P	2018P	2019P	2020P
Product Revenue							$ 25	$ 51	$ 80
Other	18	19	20	20	20	12	10	6	5
Total Revenue	**$ 18**	**$ 19**	**$ 20**	**$ 20**	**$ 20**	**$ 12**	**$ 35**	**$ 57**	**$ 85**
COGS	-	-	-	-	-	-	1	5	8
SG&A	7	7	12	13	14	20	40	50	50
R&D	27	23	31	30	25	20	15	15	15
Operating Income	$ (16)	$ (12)	$ (23)	$ (23)	$ (19)	$ (28)	$ (21)	$ (13)	$ 13
Net Income	$ (18)	$ (13)	$ (23)	$ (23)	$ (19)	$ (28)	$ (21)	$ (13)	$ 12
Diluted Shares O/S			14	19	19	20	20	21	21
Diluted EPS			**($1.60)**	**($1.20)**	**($1.00)**	**($1.45)**	**($1.05)**	**($0.65)**	**$0.60**

Source: Company filings and Gabelli & Company estimates

Plazomicin and CRE

Plazomicin is a novel aminoglycoside antibiotic that is being developed by Achaogen for the treatment of bacterial infections from multi-drug resistant (MDR) *Enterobacteriaceae*, including CRE. It is estimated that up to half of all CRE bloodstream infections are fatal. Current standard of care involves combination therapy, which often consists of a tetracycline (i.e. tigecycline), aminoglycoside, or Colistin. Colistin is a 50+ year old polypeptide antibiotic that is used as a last resort due to kidney toxicity issues. Even with combination therapy, all-cause mortality rates for CRE are estimated at 30-40%. Plazomicin was designed to overcome the mechanisms of resistance that CRE uses against older aminoglycosides.

Aminoglycosides are one of the earliest classes of antibiotics, with the first (streptomycin) being approved 70 years ago. While these drugs are effective against Gram-negative bacteria, their use has been limited due to class safety issues, including nephrotoxicity (kidney) and ototoxicity (ear). In 2009, aminoglycosides accounted for only 2-3% of both the US and global antibiotic markets. However, the emergence of MDR infections has led to renewed use of the class. Plazomicin would be the first new aminoglycoside in the US in over 30 years.

In September 2013, Achaogen and the FDA agreed to a Special Protocol Assessment (SPA) for the company's single-study open-label pivotal Phase III trial to demonstrate superiority of plazomicin for bloodstream or nosocomial pneumonia infections due to CRE. The study will enroll up to 360 patients randomized 1:1 to either plazomicin or Colistin. Patients in both groups will also be administered a second antibiotic (either tigecycline or meropenem) for combination therapy. The primary endpoint will be all-cause mortality. A meta-analysis of patients treated with a carbapenem for CRE bloodstreams found that mortality rates fell from 35% to 14% for bacterial strains that were more susceptible to the drug (based on MIC<4μg/ml), resulting in a 21% mortality rate decline. Achaogen believes that this effect could be a proxy for plazomicin and has powered the Phase III study to succeed with a 12% reduction in mortality. Achaogen expects the study to be completed in early 2017 with full enrollment but could be stopped earlier at either of two interim analysis points.

While Plazomicin has not been clinically tested in CRE, the drug did successfully demonstrate non-inferiority to levofloxacin in a Phase II cUTI study. The safety profile shows potential for the expected class risks of nephrotoxicity and ototoxicity but was otherwise consistent with the comparator. In addition to the pivotal trial, Achaogen is planning to initiate two small open-label supportive studies – a ~50 patient efficacy study expected in late 2014 and a ~70 patient safety study expected in mid-late 2015.

We believe that the Phase III program for plazomicin carries several risks that other antibiotic development programs are not exposed to, including:

- *No clinical efficacy data in CRE*. Plazomicin has demonstrated *in vitro* activity against CRE, but the drug was not tested clinically against CRE in a Phase II study. The expected effect of plazomicin on mortality is based on a hypothesis developed from a meta-analysis of carbapenem use in CRE patients.
- *Increased exposure of drug*. In Phase I and II, plazomicin was given for a maximum of five days and primarily as a single agent. In Phase III, the drug will be dosed for 7-14 days and in combination with tigecycline or meropenem. This increased exposure and use with other therapies could lead to a higher rate of adverse events and tolerability issues as compared to Phase II.
- *Slow enrollment*. CRE's account for an estimated 2.5% of Enterobacteriaceae infections, which themselves account for approximately one-fourth of bloodstream and pneumonia infections. Thus, the CRE infection rate is approximately 1 in 160 patients. Given this low prevalence of CRE rates and the need to meet other criteria (including APACHE II scores of 15-30), enrollment could be slower than anticipated.
- *Superiority endpoint*. Unlike most antibiotic studies with non-inferiority endpoints, the plazomicin Phase III study is based on the more challenging threshold of superiority.

Commercial Opportunity

According to the CDC, there are over 9,300 CRE hospital infections annually in the US. However, based on prevalence figures, Achaogen estimates that there are 30,000 cases of CRE bloodstream or pneumonia infections in the US and major EU countries each year. With superiority data for an infection that has a high mortality rate and limited treatment options, the company also expects premium pricing for plazomicin. Current branded antibiotics can cost from $3,000-4,000 for a course of treatment, but plazomicin could potentially be priced at $15,000, or 4-5x existing branded pricing. At this price point, the addressable market for plazomicin in the US and EU would be approximately $450 million.

We view this $15,000 per treatment pricing model as justifiable in assessing plazomicin's commercial potential but also recognize it as risky. The price will depend primarily on the strength of the Phase III data, and the expected approval of several new antibiotics capable of treating resistant Gram-negative bacteria over the next four years could provide competition and pricing pressure. Assuming FDA approval in early 2018, we estimate that global sales of plazomicin could approach $100 million in 2020 and reach $250-300 million at peak.

Financing

In March 2014, Achaogen went public at an IPO price of $12 per share and finished the first quarter with $84.9 million of cash and $5.5 million of debt. Most of the funding for plazomicin has come from a BARDA contract covering development for both CRE and biothreat pathogens. BARDA has committed $103.8 million to the company, of which $58.3 million remains outstanding. There is also an unexercised option for an undetermined amount associated with the open-label safety studies. Achaogen expects BARDA to evaluate awarding this option in mid-2015.

We believe that Achaogen's cash on hand and committed funding from BARDA will get the company to H2 2017. The company believes that they will have top-line Phase III data by this time but will need additional cash to launch plazomicin. We estimate that the company would need an extra $30-40 million at that time to reach profitability in 2020.

Exhibit 1 **Timeline of Upcoming Events for Achaogen**

Date	Event
Q4 2014	Initiation of supportive efficacy study for plazomicin
Mid 2015	Update on potential BARDA award option
H2 2015	Initiation of supportive safety study for plazomicin
H2 2015	First interim analysis for plazomicin Phase III (33% complete)
Mid 2016	Second interim analysis for plazomicin Phase III (67% complete)
H1 2017	Top-line data for plazomicin Phase III
Mid 2017	NDA filing for plazomicin

Source: Company filings and Gabelli & Company estimates

Valuation and Opinion

Our valuation of Achaogen is based on an 8.5x sales multiple on product revenues from plazomicin (US sales + estimated 25% royalty on ex-US sales) in 2020, the product's third year on the market. This is consistent with the multiple of sales that Cubist paid to acquired Optimer in 2013 as well the average for other recent acquisitions for acute care companies. Prior to 2020 we discount back at a 10% annual rate and also adjust the valuation to reflect the risk of approval at the NDA stage (2017) and during Phase III (2014-2016). While we normally would use a 75% probability of approval for a Phase III asset, we are using a 65% probability for Achaogen since plazomicin has not demonstrated efficacy in a Phase II trial specifically for treatment of CRE. We also include the net present value of the company's federal NOL, which was $114 million at the end of 2013.

Using this methodology, we estimate a Private Market value for Achaogen of $19 per share in 2015, growing to $38 per share in 2020. This valuation for 2015 puts the company within the $300-350 million range that we estimate for the value of a Phase III antibiotic. We note that AKAO's current market cap of $285 million is between the ranges for a Phase II and Phase III asset. While plazomicin is currently in Phase III, the remaining time to market and lack of proof-of-concept data are more consistent with a Phase II drug.

We are initiating coverage on Achoagen with a Hold recommendation. We believe that Plazomicin has the highest risk of any lead antibiotic among those from the four publicly-traded pure-play clinical and pre-commercial antibiotic companies. AKAO shares, which currently trade at a 19% discount to our 2015 PMV of $19 per share, do not provide an adequate margin of safety to compensate for the level of risk and extensive timeline for the plazomicin Phase III study.

Table 2

Achaogen, Inc.
Private Market Value Analysis
2014E – 2020P

($ in millions except per share data)	**2014E**	**2015P**	**2016P**	**2017P**	**2018P**	**2019P**	**2020P**
Product Revenue					**$ 25**	**$ 51**	**$ 80**
Valuation Multiple							8.5 x
Annual Discount	10%	10%	10%	10%	10%	10%	
Total Private Market Value	$ 384	$ 422	$ 464	$ 511	$ 562	$ 618	$ 680
Clinical Stage Discount	35%	35%	35%	20%			
Risk-Adjusted Total PMV	$ 249	$ 274	$ 302	$ 409	$ 562	$ 618	$ 680
Less: Net Debt	58	37	21	(4)	(21)	(28)	(10)
Plus: NOL (a)	27	31	34	38	42	44	42
Less: Option Payments (b)	(12)	(12)	(13)	(18)	(26)	(29)	(33)
Equity Private Market Value	$ 322	$ 330	$ 343	$ 425	$ 557	$ 605	$ 679
Shares Outstanding	18	18	18	18	18	18	18
PMV per share	**$18**	**$19**	**$19**	**$24**	**$31**	**$34**	**$38**
Current Market - Discount to PMV	*14%*	*19%*	*19%*	*36%*	*50%*	*55%*	*59%*

(a) Net present value of federal NOL carryforward
(b) After-tax payments to buy out options at PMV
Source: Company filings and Gabelli & Company estimates

APPENDIX **LATE-STAGE GRAM-NEGATIVE SPECIFIC ANTIBIOTICS**

PLAZOMICIN FOR CRE INFECTIONS ACHAOGEN

Plazomicin is a next-generation aminoglycoside from Achaogen (NASDAQ: AKAO) that is currently in Phase III for treatment of infections due to carbapenem-resistant *Enterobacteriaceae* (CRE). In the 360-patient single Phase III study, the company is looking to demonstrate superiority in all-cause mortality (primary endpoint at 28 days) for once-daily IV plazomicin compared to Colistin, an older polypeptide antibiotic. All patients will also be able to receive meropenem or tigecycline since CRE patients are often treated with combination antibiotic therapy. Top-line data are expected in 2017, but there will be interim reviews when the trial reaches one-third and two-thirds enrollment.

Plazomicin successfully completed a Phase II trial against levofloxacin for cUTI and acute pyelonephritis (AP). Two doses of plazomicin (10 and 15 mg/kg) were evaluated in the study. The combined plazomicin arms were similar to levofloxacin for the primary endpoint of microbiological eradication (MBE) rates in both the microbiologic intent-to-treat (mITT) group (58.7% plazomicin vs. 58.6% levofloxacin) and microbiologically evaluable (ME) group (88.1% vs. 81.0%). This was also seen for clinical cure rates in the mITT (69.8% vs. 65.5%) and ME (76.2% vs. 76.2%) groups. Adverse event rates for plazomicin (17.7%) were lower than for levofloxacin (27.3%). Clinically relevant mild increases (at least 0.5 mg/dl) in serum creatinine, an indicator of kidney injury, occurred in 5.2% of plazomicin and 4.5% of levofloxacin patients. These values returned to near-baseline levels in all but one plazomicin patient. Also, one plazomicin patient reported permanent tinnitus.

For the Phase III trial, plazomicin will be initially dosed at 15mg/kg and then adjusted by physicians. Also, patients will be on the drug for 7-14 days as opposed to 5 days for Phase II study.

Table C1 **Results from Plazomicin Phase II Study in cUTI and AP**

	Plazomicin 10mg	Plazomicin 15mg	Levofloxacin 750mg
Primary Endpoint – MBE at TOC			
MITT patients	6/12 (50.0%)	31/51 (60.8%)	17/29 (58.6%)
95% Confidence Interval	(21.1 - 78.9%)	(46.1 - 74.2%)	(38.9 – 76.5%)
ME patients	6/7 (85.7%)	31/35 (88.6%)	17/21 (81.0%)
95% Confidence Interval	(42.1 – 99.6%)	(73.3 – 96.8%)	(58.1 – 94.6%)
Secondary Endpoint – Clinical Cure at TOC			
MITT patients	8/12 (66.7%)	36/51 (70.6%)	19/29 (65.5%)
95% Confidence Interval	(34.9 – 90.1%)	(56.2 – 82.5%)	(45.7 – 82.1%)
ME patients	4/7 (57.1%)	28/35 (80.0%)	16/21 (76.2%)
95% Confidence Interval	(18.4 – 90.1%)	(63.1 – 91.6%)	(52.8 – 91.8%)
Safety Results			
Total Adverse Events	7/22 (31.8%)	26/74 (35.1%)	21/44 (47.7%)
Gastrointestinal AE's	4/22 (18.2%)	13/74 (17.6%)	5/44 (11.4%)

MBE – Microbiological Eradication; TOC – Test of Cure; MITT – Microbiological Intend to Treat;
ME – Microbiologically evaluable; AE – Adverse Event
Source: Company filings, publications, and poster presentations

Other Companies Mentioned:
Cubist Pharmaceuticals (CBST – NASDAQ)

I***, Kevin Kedra,*** the Research Analyst who prepared this report, hereby certify that the views expressed in this report accurately reflect the analyst's personal views about the subject companies and their securities. The Research Analyst has not been, is not and will not be receiving direct or indirect compensation for expressing the specific recommendation or view in this report.

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Important Disclosures

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Analysts' ratings are largely (but not always) determined by our "private market value," or PMV methodology. Our basic goal is to understand in absolute terms what a rational, strategic buyer would pay for an asset in an open, arms-length transaction. At the same time, analysts also look for underlying catalysts that could encourage those private market values to surface.
A **Buy** rated stock is one that in our view is trading at a meaningful discount to our estimated PMV. We could expect a more modest private market value to increase at an accelerated pace, the discount of the public stock price to PMV to narrow through the emergence of a catalyst, or some combination of the two to occur.
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