William Blair

Achaogen, Inc.

Novel Antibiotic Against CRE First Seeks Superiority in Survival: Initiating Coverage With Outperform Rating and $25 Price Target

Achaogen develops novel antibiotics at a time of tremendous need, when multi-drug-resistant (MDR), Gram-negative infections have demonstrated widespread resistance to currently available therapies.

We are initiating coverage of Achaogen with an Outperform rating and $25 price target, based on our belief that Achaogen's lead asset, plazomicin, will become the standard of care for a life-threatening indication and generate peak sales of $370 million worldwide by 2028. Plazomicin is in Phase III development for the treatment of bloodstream infections and pneumonia caused by carbapenem-resistant Enterobacteriaceae (CRE). Compared with the currently available therapies and agents in clinical development, plazomicin has the best efficacy profile against CRE, based on in vitro and in vivo data, with a favorable safety profile.

The ongoing Phase III study of plazomicin is the first pathogen-specific pivotal study that strives for superiority in overall survival. Should such a label be obtained, plazomicin would be favored over other antibiotics in the battle against CRE, and command premium pricing, in our opinion. The Phase III study evaluates plazomicin against the current standard of care, with 28-day mortality as the primary endpoint. Two interim analyses are scheduled for 2015 and 2016, with final top-line data expected during 2017. A supportive Phase II single-arm study is to be initiated during fourth quarter 2014 and read out by year-end 2015; successful data might lead to a breakthrough designation for plazomicin in CRE and create heightened excitement and confidence in the ongoing Phase III study.

We value plazomicin at $21 per share, based on our probability-adjusted net present value (NPV) model. We estimate plazomicin worldwide sales will reach $370 million in the United States and Europe by 2028. Assuming a 70% probability of success, no terminal value beyond 2031, and including net cash of $4 by year-end 2014, our probability-adjusted NPV model suggests a fair value for Achaogen of $25 at year-end 2014.

We believe a number of catalysts will drive value in the next 36 months, including: 1) first interim analysis of the Phase III study in second half 2015; 2) top-line data from the supportive study in fourth quarter 2015; 3) second interim analysis of the Phase III study in second half 2016; and 4) top-line data from the plazomicin Phase III study in first half 2017.

Achaogen, Inc., a biopharmaceutical company based in South San Francisco, California, focuses its research-and-development efforts on novel antibacterials to treat multi-drug-resistant, Gram-negative infections.

April 7, 2014
Basic Report (14-040)

Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$25.00
Symbol:	AKAO (Nasdaq)
Price:	$15.95 (52-Wk.: $13–$20)
Market Value (mil.):	$273
Fiscal Year End:	December

Estimates	**2013A**	**2014E**	**2015E**
EPS FY	$1.36	$0.69	$1.04
Sales (mil.)	$18.5	$30.0	$24.0
Valuation			
P/E	NM	NM	NM

Trading Data	
Shares Outstanding (mil.)	17.7
Float (mil.)	7.6
Average Daily Volume	411,320
Financial Data	
Total Debt/Total Capital	7.1%
Enterprise Value (mil.)	$193
Price/Book	NM

Y. Katherine Xu, Ph.D.
+1 212 237 2758
kxu@williamblair.com

Filippo Petti
+1 212 237 2741
fpetti@williamblair.com

Contents

Investment Summary

Achaogen Focuses on Developing Antibiotics Against Gram-Negative Pathogens
Founded in 2004 and based in South San Francisco, California, Achaogen is a biopharmaceutical company focused on developing antibiotic therapies for MDR, Gram-negative bacterial infections.

- ***Achaogen's lead drug candidate, plazomicin, currently in a pivotal Phase III study, is a novel aminoglycoside discovered in house.*** Plazomicin is modified from sisomicin, a naturally occurring aminoglycoside, to overcome a common resistance mechanism to the class. Plazomicin is an intravenous (IV) antibiotic currently in development for the treatment of serious bacterial infections resulting from MDR Enterobacteriaceae, including CRE. Achaogen owes Isis Pharmaceuticals milestone payments and low single-digit royalties on potential plazomicin sales due to an exclusive license of certain related intellectual property.

- ***The second class of candidates being developed belongs to the class of LpxC inhibitors, currently in pre-clinical development.*** LpxC is an enzyme essential for the synthesis of the outer membrane of Gram-negative bacteria. LpxC inhibition disrupts the integrity of the outer bacterial membrane, thus reducing its ability to protect the cell and resulting in bacterial cell death. Achaogen has developed a number of molecules with no cross-resistance to current antibiotics. Achaogen intends to develop this class of compound to combat MDR bacterium Pseudomonas aeruginosa, a current unmet need. Achaogen licensed certain intellectual property rights related to the LpxC compounds from the University of Washington and is obligated to pay small milestones and royalties.

CRE—"A Nightmare Bacteria"
Enterobacteriaceae are a family of Gram-negative bacteria typically found in the human gastrointestinal tract, and include Escherichia coli (E. coli), Salmonella, and Klebsiella. Several of these bacterial strains, including Klebsiella pneumoniae, commonly cause invasive disease, both in the community and institutional settings, but are generally susceptible to a variety of antibiotics. Over the past decade, some of these strains have become resistant to antibiotics, including carbapenems—a class of broad spectrum β-lactam antibiotics, often considered to be the "the last line of antibiotic defense" against resistant organisms.

According to the Centers of Disease Control (CDC), the first case of carbapenem-resistant Enterobacteriaceae (CRE) was described in the United States in 1999. Over the past 15 years, CRE have spread from 1 state to 46 states. In the hospital setting, CRE are recognized as difficult-to-treat infections and are associated with high mortality rates, including close to 50% of patients with bloodstream infections (BSIs) resulting from CRE. In March 2013, the director of the CDC stated that "CRE are nightmare bacteria." CRE have captured the attention of global health authorities, because unlike resistance in methicillin-resistant Staphylococcus aureus (MRSA), which involves one bacterial species facilitated by a single mechanism, CRE are complex; resistance can occur in different Enterobacteriaceae and be mediated by several mechanisms.

Carbapenem resistance has been emerging in "hot spots" throughout the world over the past few years. In the United States, CRE infections are evident in a number of major cities, including New York City (in particular, Brooklyn), Philadelphia, Detroit, Chicago, and Los Angeles. Outside the United States, CRE is becoming endemic in countries such as Italy, Greece, Israel, Brazil, and India. While infections are typically limited to large metropolitan hospitals, CRE's ability to quickly spread horizontally (move into new regions) and gain resistance to current therapies has led to rapidly increasing incidence.

Plazomicin Is Set to Target Life-Threatening Infections Caused by CRE
Given the highly competitive landscape in various areas of antibiotic development, including complicated urinary-tract infection (cUTI), Achaogen elected to develop plazomicin for the most-difficult indication where it could have the most impact: life-threatening BSIs and pneumonia caused by the toughest of CRE bugs.

- ***In vitro activity among the best against CRE.*** Plazomicin has demonstrated potent activity in in vitro against CRE-bacterial isolates.

- ***In vivo efficacy superior to current standard of care.*** Plazomicin has shown efficacy against CRE in multiple animal models. In addition, plazomicin was consistently more potent than the current standard of care in these in vivo models at doses equivalent to those used clinically.

- ***Phase II cUTI study suggests a similar efficacy and safety to levofloxacin.*** In the cUTI study, patients were treated for five days, and plazomicin demonstrated similar efficacy to levofloxacin. Plazomicin was safe and tolerable, with one case of mild nephrotoxicity (i.e., slightly elevated serum creatinine) and two cases of ototoxicity (i.e., case of mild transient vertigo and a mild unilateral tinnitus).

We believe plazomicin possesses a promising profile for the treatment of CRE infections, given the drug's in vitro and in vivo data in CRE, as well as efficacy and safety data from the Phase II study in cUTI, an indication where the majority of infections are caused by Enterobacteriaceae.

Phase III Design: The First Pathogen-Specific Study That Strives for Superiority in Survival
In first quarter 2014, Achaogen initiated the Phase III CARE (Combating Antibiotic-Resistant Enterobacteriaceae) study evaluating plazomicin versus standard of care for the treatment of patients with CRE BSIs and CRE pneumonia. Total enrollment is 360 patients with 1:1 randomization. CARE represents the first registrational study to evaluate an antibiotic versus its comparator with a superiority endpoint in survival; typical antibiotic Phase III studies use non-inferiority designs assessing relative efficacy. Should the Phase III study be successful and plazomicin obtain a label with superiority in survival, we believe plazomicin would be the preferred agent for the treatment of CRE and command premium pricing.

We Set the Probability of Success for the Phase III Study at 70%
While we believe plazomicin is a viable antibiotic for the treatment of CRE, several arguments must be taken into consideration when assessing its overall likelihood of success. Several of our rationales for assigning the program a 70% probability of success include:

- ***The potency of plazomicin in CRE is based on in vivo and in vitro studies, as discussed above; translation to humans is predicted but needs to be demonstrated.*** While plazomicin is comparable to levofloxacin for safety and efficacy in cUTIs, there are no prior dedicated studies investigating the effects of plazomicin in CRE. Although we are relatively confident that efficacy of antibacterials generally translates from in vivo models to the clinic, it still needs to be demonstrated in this case. We note that Achaogen will initiate a supporting single-arm Phase II study in CRE in late 2014 and data should read out in late 2015. This study should provide the first data on plazomicin's activity in CRE and if successful should create heightened excitement and confidence in the ongoing Phase III CARE study.

- ***Phase III enrollment is projected to take three years, but the emerging epidemiology is a moving target.*** The incidence of CRE has been increasing over the past few years especially in certain hot spot areas; however, the exact timeline of enrollment is difficult to predict as the epidemiology data is still developing.

- ***The statistical assumptions for the Phase III study are based on a meta-analysis of three observational studies.*** There is limited data in literature on mortality rates from CRE and as discussed in detail herein, the Phase III study is based on a meta-analysis describing mortality outcomes from 309 patients infected with carbapenemase-producing Enterobacteriaceae. The meta-analysis classified outcomes of these patients into two groups, resistant or sensitive to carbapenems, and observed that the absolute mortality difference between the two groups was 21% (60% relative difference). Based on such data, the underlying assumption for the CARE study is that plazomicin treatment should afford patients a similar mortality benefit to those in the sensitive group in the meta-analysis, which is a 21% absolute mortality reduction from the current standard of care.

- ***Although the Phase III study is based on a meta-analysis, a margin of safety is built in, thereby increasing the probability of success, in our opinion.*** The Phase III study is powered at 70% to detect an absolute reduction in mortality of 12% (35% relative reduction). This assumption appears conservative as compared with the observed mortality reduction of 21% (60% relative reduction) demonstrated by the meta-analysis. This difference allows for a reasonable margin of safety, thus increasing the probability of success, in our opinion.

- ***Interim analyses are built in to provide a potential opportunity to adjust sample size if necessary, ensuring power of the study.*** There will be two unblinded interim analyses occurring when 33% and 67% of the patients in the study have reached day 28 (the end of the study). A data monitoring committee will review the data and determine if the study should be stopped based on efficacy or futility. These interim analyses might also help determine whether more patients will need to be enrolled to ensure power of the study.

- ***A companion diagnostic will be employed to ensure plazomicin plasma and lung concentration reaches bactericidal levels, thereby ensuring maximum efficacy in every patient.*** Since plazomicin is renally excreted, dosing will be individually optimized using a diagnostic to ensure sufficient drug plasma and lung concentration to combat infections. Pharmacometric modeling developed at Achaogen predicts that 92% of patients should be able to achieve sufficient drug levels in the blood or the lung that are effective against their CRE infection.

- ***Phase III study is enriched with patients who will most likely see a mortality benefit from plazomicin treatment.*** To better assess disease severity, all patients will be evaluated using the APACHE II score, which ranges from 0 to 71, with 71 being most severe. Enrolled patients will have APACHE II scores ranging from 15 to 30. We highlight this because it ensures that enrolled patients are neither too healthy nor too sick, increasing the odds of demonstrating a mortality benefit.

- ***The safety profile remains to be evaluated when used for a longer duration of treatment in a sicker patient population.*** While the Phase II study in cUTI demonstrated a safe and tolerable profile of plazomicin for 5 days of treatment, the safety profile requires further evaluation in the Phase III study where treatment duration is increased to 7-14 days, and the patient population is much sicker. Undoubtedly, the risk/benefit profile will be different in this sicker population, with patients and regulators willing to accept greater risk if a significant mortality benefit is demonstrated.

- ***High risk, high reward: The primary endpoint of mortality is bold and novel to antibiotics.*** Unlike other antibiotics, the registrational trial will strive for superiority in survival. Should such a label be obtained, plazomicin should be preferentially used in the labeled indication, and command premium pricing, in our opinion.

Phase II Supportive Study Could Boost the Entire Plazomicin Program
Achaogen plans to initiate a 50-patient, single-arm Phase II supportive study during fourth quarter 2014 and report data by year-end 2015. The study will assess clinical and microbiological endpoints, but not survival endpoints.

We believe the goals of the study are a few fold: 1) the 50 patients will constitute part of plazomicin's overall safety database; 2) the study plans to enroll a broader CRE patient population, including patients with cUTI, cIAI (complicated intra-abdominal infections) and colistin-resistant infections in addition to the BSI and pneumonia eligible for the Phase III study, so as to gain broader experience of plazomicin in various CRE infections; 3) successful data in late 2015 could generate excitement, boost confidence and help accelerate enrollment in the Phase III CARE study; and 4) successful data could also serve as potential supportive data should Achaogen request Breakthrough Therapy designation for plazomicin for the treatment of CRE.

As a result, we believe results from the Phase II supportive study are a significant catalyst for the plazomicin program in late 2015.

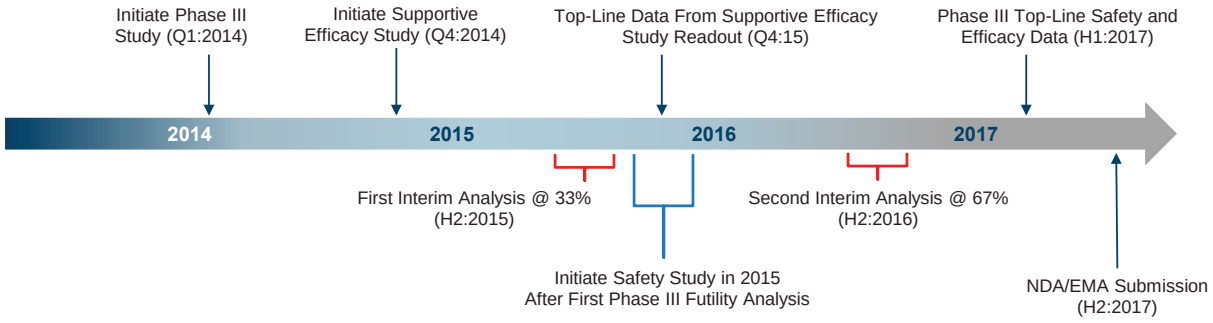
Composition of Plazomicin's Registration Package; Approval Second Half 2018
The plazomicin registration package for serious CRE infections includes the Phase III CARE study, the Phase II supportive study, as well as a third study focused on safety. We anticipate regulatory submissions by year-end 2017, resulting in a potential approval of plazomicin by second half 2018. On the efficacy side, a successful CARE study with data from the supportive Phase II study is sufficient for approval. On the safety side, the CARE study, in conjunction with the 50-person supportive efficacy Phase II study (expected in fourth quarter 2015) and a 70-person safety study (expected in first half of 2017), should allow Achaogen to meet the 300-person safety database requirement for approval.

Plazomicin Commercialization Strategy: Taking on North America and Partnering Internationally
Achaogen plans to commercialize plazomicin either on its own or with a partner in the United States and Canada. The target will be hospitals where many CRE outbreaks originate. At this stage, we assume commercialization will occur alone and consist of a 35-person salesforce.

Outside the United States, Achaogen intends to license product rights to global or regional commercialization partners. We look to the planned interim analyses as possible points of entry for a partner. In our model, we project that Achaogen will receive 30% royalties on sales of plazomicin and up to $150 million in potential regulatory and commercial milestones.

Key Catalysts Spread Out in Coming Years Should Continue to Drive Awareness of Plazomicin
Achaogen has devised an efficient registrational strategy to push plazomicin on the market as quickly as is practical, in our opinion. Top-line data are expected in 2017; however, two interim analyses expected in second half 2015 and second half 2016 will act as key catalysts over the next several years along with top-line data from the Phase II supportive study by year-end 2015. Regulatory filing for plazomicin is expected in the second half of 2017, and we anticipate U.S. approval by the FDA during second half 2018. We illustrate plazomicin's development timeline in exhibit 1.

Exhibit 1
Achaogen, Inc.
Plazomicin Development Timeline



Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

Existing Cash Together With Government Funding Should Sustain Operations Through CARE Data Readout in Early 2017

We estimate Achaogen's cash position at approximately $81 million as of the end of first quarter 2014. Based on the existing contract with BARDA (Biomedical Advanced Research and Development Authority within the U.S. Department of Health and Human Services), an additional $60.4 million in funding is expected. Further, if BARDA elects to exercise its third option on plazomicin, additional grants will be available, which may fund the 70-patient safety study expected to be initiated in late 2015/early 2016 following the first interim analysis of the Phase III CARE study. Taken as a whole, the existing cash resources as well as the government funding should provide Achaogen sufficient cash through the 2017 Phase III CARE readout.

Competitive Landscape in the Treatment of CRE

At present, only three drugs, the generics colistin and gentamicin as well as Pfizer's Tygacil (tigecycline), are used for the treatment of CRE, with limited effectiveness and mortality rates around 40%. Several companies are developing antibiotics or antibiotic combinations that could target CRE; however, only the Medicines Company appears to be specifically focused on the development of its combination antibiotic, Carbavance, for the treatment of CRE. Other companies that may compete against Achaogen include AstraZeneca/Forest Laboratories, Cubist Pharmaceuticals, and Merck. We discuss the clinical candidates from these companies in later sections. Despite the competition, we believe that Achaogen's Phase III study, which includes a superiority endpoint on overall survival, will provide the company with a dramatic competitive advantage, should the study be successful.

William Blair Revenue Model for Plazomicin Sales in the United States and EU

We illustrate our plazomicin revenue model in exhibit 2 and worldwide sales estimates in exhibit 3, on page 9. An estimated 110,000 cases of confirmed CRE infections occurred within the United States and the five major markets in the European Union in 2013; we estimate that 55% of these diagnosed cases occurred in the United States. Roughly 25% of these CRE infections were either BSIs or pneumonia.

- ***Competitive market share in the treatment of CRE.*** As illustrated in exhibit 2, on the following page, we peg peak penetration of plazomicin at about 65%, both in the United States and in Europe, based on our expectation that plazomicin obtains a favorable label regarding superiority in survival benefit for the indication.

- ***Pricing.*** We price plazomicin at about $16,000 per course of therapy in the United States at launch in 2018, and we apply a number of discount factors, including a 99% compliance rate, 5% discontinuation rate, and a gross-to-net conversion rate of 12%. In addition, we forecast

an annual 4% price increase in the United States. In Europe, we estimate plazomicin will price at about $14,000 per course of therapy at launch in 2018. We assume similar compliance and discontinuation rates in Europe for plazomicin, but include a gross-to-net conversion rate of 8%. We assume flat pricing for plazomicin in the European Union.

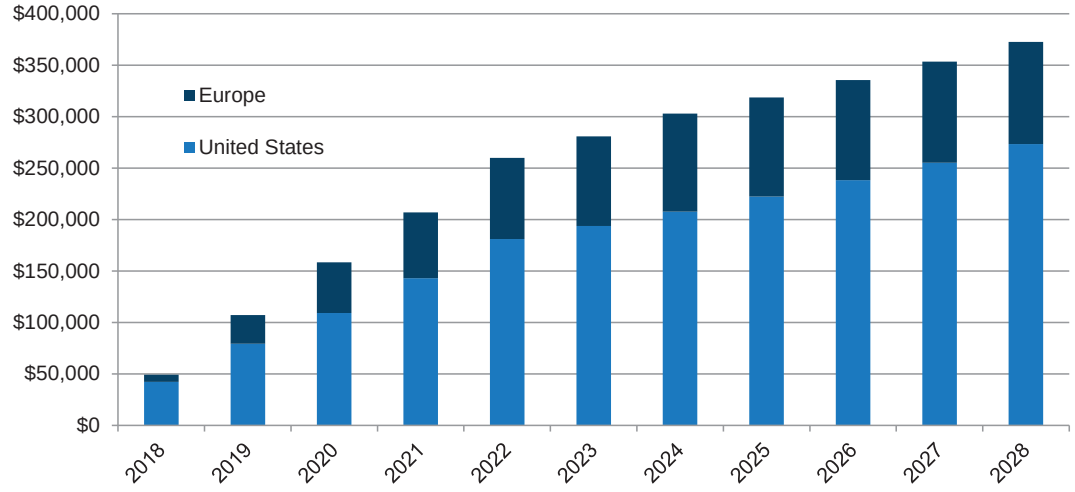
- ***Our revenue projection.*** We therefore derive U.S. peak sales of about $305 million in 2031 and approximately $100 million in Europe in 2028, with peak worldwide sales of roughly $370 million in 2028. Plazomicin's composition of matter '596 patent expires in November 2028; however, the company has noted that the United States Patent and Trademark Office (USPTO) has determined that the '596 patent is entitled to a 2.5 year patent term adjustment extending patent expiration until June 2031. Achaogen also notes that the '596 patent may further benefit from a Hatch-Waxman extension in the United States, which may extend the patent protection up to a maximum of five additional years depending upon the date of plazomicin's potential approval in the United States. Outside the United States, we believe plazomicin's composition of matter patents are expected to extend to at least 2031.

Exhibit 2
Achaogen, Inc.
William Blair Revenue Model for Plazomicin

		2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
United States: CRE	60,500	16,172	16,657	17,157	17,672	18,202	18,748	19,310	19,890	20,486	21,101	21,734
% BSI and pneumonia	25%											
% eligible	95%											
Growth of incidence	3%											
Penetration		*20%*	*35%*	*45%*	*55%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*
Number of Patients Treated		3,234	5,830	7,721	9,719	11,831	12,186	12,552	12,928	13,316	13,716	14,127
Average Days of Tx		10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Total Number of Tx Days		32,344	58,301	77,207	97,195	118,312	121,862	125,518	129,283	133,162	137,156	141,271
Net Price of Plazomicin, daily		1,307	1,359	1,414	1,470	1,529	1,590	1,654	1,720	1,789	1,860	1,935
Price increase	4%											
Gross-to-net discount	12%											
Compliance	99%											
Discontinuation	5%											
Sales from CRE Tx - U.S.		**42,277,226**	**79,252,887**	**109,151,605**	**142,906,133**	**180,913,967**	**193,795,042**	**207,593,249**	**222,373,888**	**238,206,909**	**255,167,241**	**273,335,149**
Total Sales - U.S.		**42,277,226**	**79,252,887**	**109,151,605**	**142,906,133**	**180,913,967**	**193,795,042**	**207,593,249**	**222,373,888**	**238,206,909**	**255,167,241**	**273,335,149**
Europe: CRE	49,500	11,819	11,937	12,057	12,177	12,299	12,422	12,546	12,672	12,799	12,927	13,056
% BSI and pneumonia	25%											
% eligible	90%											
Growth of incidence	3%											
Penetration		*5%*	*20%*	*35%*	*45%*	*55%*	*60%*	*65%*	*65%*	*65%*	*65%*	*65%*
Number of Patients Treated		591	2,387	4,220	5,480	6,765	7,453	8,155	8,237	8,319	8,402	8,486
Average Days of Tx		10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Total Number of Tx Days		5,910	23,875	42,199	54,798	67,645	74,533	81,551	82,367	83,190	84,022	84,863
Net Price of Plazomicin, daily		1,168	1,168	1,168	1,168	1,168	1,168	1,168	1,168	1,168	1,168	1,168
European discount to U.S. (at launch)	85%											
Price increase	0%											
Gross-to-net discount	8%											
Compliance / Discontinuation	99%											
Discontinuation	5%											
Sales from CRE Tx - Top 5 EU		**6,903,025**	**27,888,222**	**49,292,433**	**64,009,745**	**79,016,474**	**87,061,787**	**95,260,106**	**96,212,707**	**97,174,834**	**98,146,582**	**99,128,048**
Total Sales - Top 5 EU		**6,903,025**	**27,888,222**	**49,292,433**	**64,009,745**	**79,016,474**	**87,061,787**	**95,260,106**	**96,212,707**	**97,174,834**	**98,146,582**	**99,128,048**
Total Sales - U.S. and EU		**49,180,251**	**107,141,109**	**158,444,038**	**206,915,877**	**259,930,441**	**280,856,829**	**302,853,354**	**318,586,595**	**335,381,743**	**353,313,823**	**372,463,196**

Source: William Blair & Company, L.L.C. estimates

Exhibit 3
Achaogen, Inc.
William Blair Estimates for Worldwide Sales of Plazomicin
(dollars in thousands)



Source: William Blair & Company, L.L.C. estimates

Outperform Rating Based on Market Potential of Plazomicin in the Treatment of CRE, With Potential Upside

Our Outperform rating is centered on our belief that plazomicin will become the standard of care for the treatment of CRE infections related to BSIs and pneumonia, based on its potential label indicating superiority in survival benefit.

Potential sources of major upside to our revenue estimate include the following:

- ***Empirical use of plazomicin which could add an additional $100 million in sales in 2028:*** We do not include any sales of plazomicin as an empirical agent (treatment based on the physician's experience and observations for the initial two to three days before definitive identification of the infective bacteria can be made) in our model. In 2013, about 4 million people within the United States and the five major markets in the European Union were treated empirically for BSIs or pneumonia. Of these empirically treated patients, roughly 850,000 were consulted by infection disease physicians, representative of more-complicated cases or serious infections including MDR infections. Further, in certain "hot spot" areas where patients are at high risk of CRE infections, the likelihood of plazomicin being used as an empirical agent rises dramatically. Assuming a low-single-digit market penetration into this segment, and 2-3 days of treatment per patient, we estimate plazomicin could achieve additional worldwide sales of over $100 million in 2028.

- ***Upside to net U.S. pricing:*** We assume plazomicin is priced at an average per-course cost of roughly $16,000 in the United States. Our pricing assumption is based on the estimate from a 2012 study of over 5,500 U.S. patients that showed the average incremental per-patient hospital cost for an antibiotic-resistant, healthcare-associated infection was over $15,000, as compared with infections susceptible to antibiotics. However, we believe that there could be upside to our pricing assumptions following the recent introduction of the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act into Congress. Essentially, the DISARM bill would provide Medicare add-on payments for antibiotics used in the inpatient setting to treat resistant pathogens associated with high rates of mortality and are classified as an unmet medical

need, such as CRE. We believe the legislation, which would allow hospitals to be reimbursed instead of penalized for the use of high-cost antibiotics to treat these infections, could lead to a more favorable pricing and reimbursement scenario for plazomicin than our current estimates.

- ***Sales in territories outside the United States and EU are an upside to our estimates.*** We have only included revenues for plazomicin from the United States and Europe in our model. Revenues outside these areas, in countries such as Israel, Brazil, India, China, and other regions where CRE is endemic, would be upside to our estimates.

Valuation: 12-Month Price Target of $25

In building a probability-adjusted NPV model, we estimate the peak sales of a given drug candidate, its probability of advancing to the next stage of development and eventually reaching the market, and the company's share of revenue and expenses depending on the commercialization plan and/or structure of partnerships, if any. We then calculate the cash flows after adjusting all revenues and expenses with respective cumulative probabilities for each stage. The cash flows are then discounted back using an industry-specific weighted average cost of capital (WACC) of 10%-12% to arrive at a probability-adjusted NPV for each drug candidate. Once we determine the NPV for each candidate, we then add net cash and other costs, which include expenses not directly associated with the development of the clinical candidates, to arrive at a fair value estimate for a stock.

In exhibit 4, we summarize our sum-of-the-parts valuation for Achaogen. Plazomicin represents $21 per share in valuation, with $15 associated with its commercial prospects in the United States and $6 in Europe. In addition, we include $4 in net cash per share at year-end 2014.

We assume peak sales of plazomicin to be roughly $290 million in the United States and roughly $100 million in Europe. In the United States, we factor in a 35-person commercial organization at Achaogen to market plazomicin; for Europe, we project that Achaogen will license the commercial rights to plazomicin to a partner and receive 30% royalties on EU sales.

We do not assign any valuation for Achaogen's preclinical pipeline assets, specifically the company's antipseudomonal programs.

Exhibit 4
Achaogen, Inc.
Sum-of-the-Parts Fair Value
(dollars in thousands, except shares)

Drug	Peak Sales	Stage of Development	Estimated Launch Date	Probability of Commercialization	Percentage of Sales to Company	Probability-Adjusted NPV	Value Per Share	Percentage of Fair Value
Plazomicin—United States	$289,456	Phase III	H2:2018	70%	100%	$270,056	$15.10	61.3%
Plazomicin—Europe	$99,128	Phase III	H1:2019	70%	30% Royalty	$103,352	$5.78	23.5%
Subtotal						**$373,407**	**$20.88**	**84.7%**
Net Cash at Year-End 2014						$72,274	$4.04	16.4%
Net Present Value of Additional Gain (Loss)*						($5,000)	($0.28)	(1.1%)
Sum-of-Parts Fair Value						**$440,682**	**$24.65**	**100.0%**

* Includes costs not directly related to programs above
Sources: Company reports and William Blair & Company, L.L.C. estimates

Key Biotech Companies in the Antibiotic Space

Achaogen is one of several companies focused on the development of novel antibiotics for the treatment of bacterial infections. We summarize these companies, their lead candidates, and valuations in exhibit 5.

Exhibit 5
Biotechnology Companies Focused on Clinical Development of Antibiotics
(dollars in millions)

Company	Ticker	Market Cap*	Enterprise Value *	Lead Clinical Asset(s)	Stage of Development	Lead Indication(s)	Next Catalyst
Cubist Pharmaceuticals	CBST	$5,571	$5,113	tedizolid; CXA-201	Under FDA Review; Phase III	ABSSSI; cUTI, cIAI	PDUFA action date of June 20, 2014; Submit NDA for cUTI and cIAI in first half 2014
Medicines Co.	MDCO	$1,621	$1,419	oritavancin; Carbavance	Under FDA Review; Phase III	ABSSSI; cUTI, Gram-negative MDR	PDUFA action date of August 6, 2014
Cempra, Inc.	CEMP	$385	$244	solithromycin	Phase III	CABP	Data from first Phase III expected in mid-2014
Durata Therapeutics	DRTX	$374	$295	dalbavancin	Under FDA Review	ABSSSI	PDUFA action date of May 26, 2014
Tetraphase Pharmaceuticals	TTPH	$299	$91	eravacycline	Phase III	cUTI, cIAI	Interim data from cUTI Phase III expected in mid-2014
Cellceutix Corporation	CTIX	$180	$172	brilacidin	Phase IIb	ABSSSI	Complete enrollment in Phase IIb by early 2015

* As of end of close, April 2, 2014

ABSSSI: acute bacterial skin and skin structure infections; cUTI: complicated urinary tract infections; cIAI: complicated intra-abdominal infection; MDR: multi-drug-resistant; CABP: community-acquired bacterial pneumonia
PDUFA: Prescription Drug User Fee Act
Sources: Company reports, FactSet, ClinicalTrials.gov, and William Blair & Company, L.L.C.

Recent Transactions Highlight Renewed Interest in Antibiotics

Several antibiotic-focused companies have been strategically acquired over the past year, including Trius Therapeutics for $707 million ($818 million including the assigned contingent value right) and Optimer Pharmaceuticals for $535 million ($801 million including the contingent value right) by Cubist Pharmaceuticals in July 2013. In December 2013, privately held Rempex Pharmaceuticals was acquired by the Medicines Company for $474 million, which includes $334 million in potential milestones.

Key Catalysts to Drive Value Over the Next 12 to 36 Months

In exhibit 6, we summarize key upcoming events for Achaogen. In fourth quarter 2014, a supportive study is expected to begin, on the heels of the recently initiated Phase III study. In second half 2015, we anticipate: 1) first interim analysis, 2) top-line data from the supportive efficacy study, and 3) the initiation of the second safety study. In second half 2016, the second interim analysis is expected. In 2017, we anticipate top-line data from the Phase III in the first half followed by regulatory submissions in the second half, with approval anticipated in 2018.

Exhibit 6
Achaogen, Inc.
Clinical Development Timeline and Milestones

Drug	Plazomicin	LpxC Inhibitors	Antibacterial Antibody
Indication	**CRE-bacterial BSIs and pneumonia**	**Gram-negative pathogens**	**Gram-negative pathogens**
Class	**Aminoglycoside**	**LpxC**	**--**
Partner			
Q1:14	Initiate Phase III study of plazomicin vs. colisitin in CRE infections (N=360)		
Q2:14			
Q3:14			
Q4:14	Initiate Phase II supportive efficacy study (N=50)		
H1:15		File potential IND	File potential IND
H2:15	First Phase III interim analysis; top-line data from Phase II supportive efficacy study; initiate Phase II safety study (N=70)		
H1:16			
H2:16	Second Phase III interim analysis		
H1:17	Phase III top-line data		
H2:17	Submit NDA for plazomicin		
H1:18			
H2:18	FDA approval and U.S. launch of plazomicin		

Highlighted cells: events likely to affect the stock price
Sources: Company reports and William Blair & Company, L.L.C. estimates

Experienced Management Team

Achaogen is led by an experienced management team whose executives have successful track records. In exhibit 7, we summarize the key experience of the top executives.

Exhibit 7
Achaogen, Inc.
Management Team

Management	Position	Previous Experience
Kenneth J. Hillan, M.B., Ch.B.	Chief Executive Officer, Chief Medical Officer, and Director	Senior vice president–clinical development and inflammation at Genentech; Vice president–immunology, tissue growth, and repair at Genentech; Vice president–development sciences and vice president–research operations and pathology at Genentech
Becki Filice	Senior Vice President of Development Operations and Portfolio Management	Senior director–project excellence in global development at Genentech; Project portfolio management in product development at Genentech
Derek A. Bertocci	Senior Vice President and Chief Financial Officer	Senior vice president and CFO at Accuray Incorporated; CFO at BioForm Medical, Inc; CFO at Laserscope; CFO at VISX Incorporated
Christine Murray	Vice President of Regulatory Affairs	Senior director–regulatory affairs at Alexza Pharmaceuticals, Inc.; Director and senior director of global regulatory affairs department at Gilead Sciences, Inc.; Regulatory affairs at Smithkline Beecham Pharmaceuticals

Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

Key Risks to Our Outperform Rating and Price Target

Key risks to our Outperform rating and price target include: 1) Phase III study assumptions are based on meta-analyses in addition to in vitro and in vivo animal studies; 2) no prior study has been conducted on the effects of plazomicin in patients with CRE-related BSIs or pneumonia; 3) serious adverse events may increase with exposure; 4) enrollment is hard to track and estimate because the target population is rare; 5) the CRE market may be smaller than expected and may be difficult to penetrate; 6) a companion diagnostic from ARK Diagnostics is required that must receive regulatory approval; 7) if highly priced, reimbursement may be difficult or hindered; and 8) financing risk exists.

Understanding Antibiotics

Background on Antibiotics

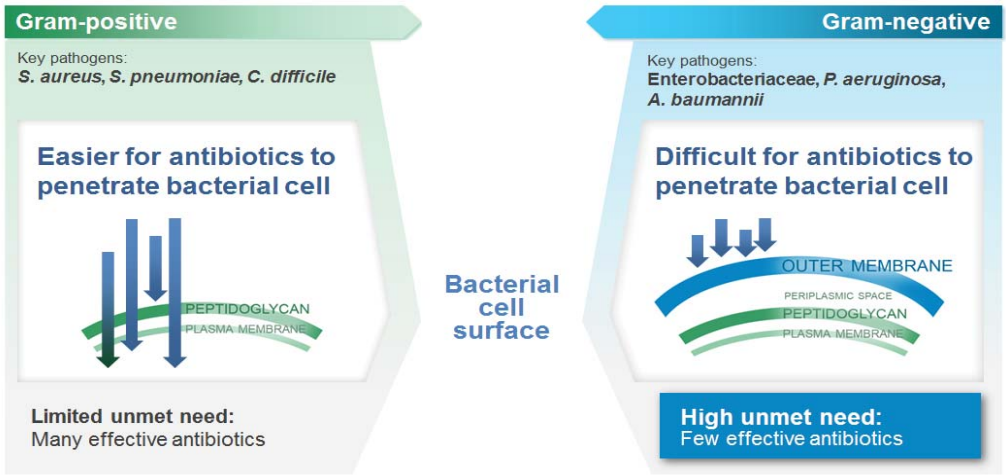
Antibiotics, or antibacterials, are drugs used to treat infections that are caused by bacteria. Before the introduction of the first commercial antibiotics during the 1930s (Prontosil, a sulfonamide), bacterial infections were often life threatening, and invasive surgery was accompanied by a high risk of complications. Since then, use of antibiotics for treatment and prevention has become common practice. According to IMS Health, over 265 million courses of antibiotics were prescribed in the United States alone in 2012; in 2013, sales of antibiotics globally were $40.2 billion, ranking fifth overall among therapeutic areas.

Gram-Positive Versus Gram-Negative Bacteria

There are two main varieties of bacteria, namely Gram-positive and Gram-negative. The designation is based solely on how they behave in a common laboratory staining test referred to as the Gram stain test, which was developed be Hans Christian Gram. Gram-positive bacteria are surrounded by a single lipid membrane and a thick cell wall made of peptidoglycan, whereas Gram-negative bacteria are encircled by two lipid membranes separated by a thinner cell wall. As a result, following the addition of the crystal violet staining, Gram-positive bacteria appear blue or purple, and following

the addition of a counterstain to the crystal violet staining, while Gram-negative bacteria appear pink or red. We illustrate the different membrane structures of Gram-positive and Gram-negative bacteria in exhibit 8.

Exhibit 8
Structural Differences Between Gram-Positive and Gram-Negative Bacteria



Source: Achaogen, Inc.

Gram-negative pathogens constitute the majority of institutional infections. According to a 2007 study by Vincent et al. *(JAMA,* 2009 302(21) pp. 2323-29), approximately 54% and 41% of bacterial infections in hospital intensive care units worldwide were caused by Gram-negative and Gram-positive pathogens, respectively, with the remaining 5% caused by other types of bacteria.

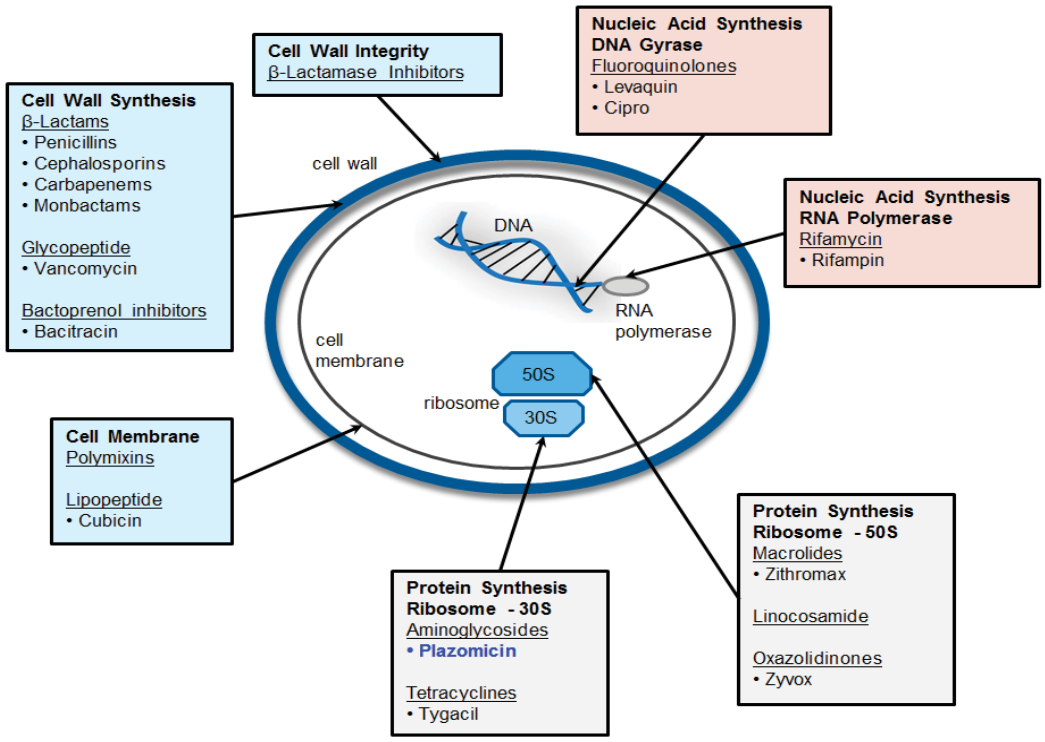
Antibiotic Classes by Mechanism of Action

There are about two dozen classes of antibiotics approved for the treatment of bacterial infections, which span eight various modes of actions. Some classes target the bacterial cell wall or cell membrane, while others target protein or nucleic acid synthesis.

For instance, the most widely used class of antibiotics, the β-lactams, which include penicillins, cephalosporins, carbapenems, and monobactams, function by inhibiting cell wall synthesis. Polymyxins and lipopeptides target the cell membrane. Pfizer's blockbusters Zithromax (azithromycin) and Zyvox (linezolid) bind to the 50S subunit of the bacterial ribosome, while tetracyclines and aminoglycosides bind the 30S subunit, both interfering with protein synthesis. The broad-spectrum fluoroquinolones, which include blockbusters Cipro (ciprofloxacin) from Bayer and Levaquin (levofloxacin) from Johnson & Johnson, function by inhibiting the two type II topoisomerase enzymes, namely DNA gyrase and topoisomerase IV, which are necessary for DNA synthesis.

We illustrate the various modes of actions of antibiotics in exhibit 9, and summarize the various classes of antibiotics and their select attributes in exhibits 10a and 10b.

Exhibit 9
Antibiotics Classification and Mechanisms of Actions



Sources: Adapted from Essential Biochemistry (Wiley), and William Blair & Company, L.L.C.

Exhibit 10a
Antibiotics by Mechanisms

Mechanism of Action	Class	Subclass	Example(s)	Type of Action	Spectrum
Cell Wall Synthesis	Penicillins	β-Lactamase-sensitive	penicillin G, penicillin V	bactericidal	Narrow - Gram-positive
		Aminopenicillins	amoxicillin, ampicillin		Moderate
		β-Lactamase-resistant	methicillin, oxacillin, dicloxacillin		Narrow - Gram-positive
		Antipseudomonal (extended-spectrum)	carbenicillin, ticarcillin, piperacillin		Moderate
	β-Lactamase inhibitors (BLIs)		clavulanic acid, sulbactam, tazobactam, **avibactam, MK-7655, CB-618**	bactericidal	--
	Cephalosporins	1st and 2nd generations	cefazolin, cefoxitin, cefuroxime, cefaclor, cefotetan	bactericidal	Moderate
		3rd - 5th generations	ceftriaxone, cefotaxime, Omnicef (cefdinir), cefepime, Teflaro (ceftaroline fosamil)		Broad
	Carbapenems		imipenem, meropenem, etrapenem, doripenem	bactericidal	Broad
	Monobactams		Cayston (aztreonam), **BAL30072**	bactericidal	Narrow - Gram-negative
	Bactoprenol inhibitors		bacitracin	bactericidal	Narrow - Gram-positive
	Glycopeptide		vancomycin, Vibativ (telavancin), **dalbavancin, oritavancin**	bactericidal	Narrow - Gram-positive
	Combinations	Aminopenicillin / BLI	Augmentin (amoxicillin / clavulanic acid)	bactericidal	Broad
		Antipseudomonal penicillin / BLI	Zosyn (piperacillin / tazobactam), Unasyn (ampicillin / sulbactam)		Broad
		Cephalosporin / BLI	**CXA-201 (ceftolozane / tazobactam), CAZ-104 (ceftazidime / avibactam)**		Broad
		Carbapenem / BLI	**Carbavance (biapenem / RPX7009), imipenem / MK-7655**		
		Carbapenem / dehydropeptidase inhibitor	Primaxin (imipenem / cilastatin)		Broad
Cell Membrane	Polymyxins		colistin (polymyxin E), polymyxin B	bactericidal	Narrow - Gram-negative
	Lipopeptide		Cubicin (daptomycin)**, surotomycin**	bactericidal	Narrow - Gram-positive

Bold: investigational therapies currently in clinical development

Sources: Company reports, Merck Manual, and William Blair & Company, L.L.C.

Exhibit 10b
Antibiotics by Mechanisms

Mechanism of Action	Class	Subclass	Example(s)	Type of Action	Spectrum
Protein Synthesis Inhibitors					
30S Subunit Inhibitors	Aminoglycosides	-mycin (*Streptomyces*)	streptomycin, neomycin, amikacin, Tobi (tobramycin)	bactericidal	Broad
		-micin (*Micromonospora*)	gentamicin, sisomicin, **plazomicin (ACHN-490)**		Narrow - Gram-negative
	Tetracyclines	Tetracyclines	doxycycline, minocycline	bacteriostatic	Broad
		Glycylcycline	Tygacil (tigecycline)		
		Fluorocycline	**eravacycline (TP-434)**		
50S Subunit Inhibitors	Macrolides		Zithromax (azithromycin), **solithromycin (CEM-101)**	bacteriostatic	Narrow - Gram-positive
	Linocosamide		clindamycin	bacteriostatic	Narrow - Gram-positive
	Streptogramins		Synercid (quinupristin / dalfopristin)	bactericidal	Narrow - Gram-positive
	Peptidyl transferase	Amphenicols	chloramphenicol	bacteriostatic	Broad
	Oxazolidinones		Zyvox (linezolid), **tedizolid (TR-701), radezolid**	varies	Narrow - Gram-positive
Folic Acid Synthesis Inhibitors	Sulfonamides		Prontosil (sulfanilamide), sulfadiazine	bacteriostatic	Broad
	Dihydrofolate reductase inhibitor		trimethoprim		
	Combination		Bactrim (trimethoprim / sulfamethoxazole, TMP-SMX)		
DNA Synthesis Inhibitors	Fluoroquinolones		Cipro (ciprofloxacin), Levaquin (levofloxacin), **delafloxacin**	bactericidal	Broad
RNA Synthesis Inhibitors	Rifamycin		rifampicin (rifampin), rifabutin, rifapentine	bactericidal	Narrow - Gram-positive,
RNA Polymerase Inhibitors	Lipiarmycin		Dificid (fidaxomicin)	bactericidal	Narrow - Gram-positive
Mycolic Acid Synthesis	Isoniazid			varies	Narrow - mycobacteria

Bold: investigational therapies currently in clinical development
Sources: Company reports, Merck Manual, and William Blair & Company, L.L.C.

Further Criteria for Classifying Antibiotics

Besides modes of actions, antibiotics are also categorized based on their spectrum of activity, cidal or static, microbiological activity, susceptibility, and resistance.

- ***Spectrum:*** Antibiotics that are effective against a wide array of bacteria, including both Gram-positive and Gram-negative organisms, are referred to as broad-spectrum agents, while antibacterials that have activity against a limited number of organisms are considered to be narrow-spectrum. Narrow-spectrum antibiotics are typically selected if a specific pathogen is suspected or confirmed. Examples of narrow-spectrum antibiotics that target Gram-positive and Gram-negative organisms include Cubist's Cubicin (daptomycin) and Achaogen's plazomicin, respectively.

- ***Cidality:*** Antibiotics are typically classified based on their biological effect on the pathogens, either as bactericidal agents or bacteriostatic agents. While bactericidal antibiotics directly kill the pathogen, bacteriostatic antibiotics halt the bacterial growth and rely on the human immune system to eventually clear the infection.

- ***Potency:*** Commonly referred to as microbiological activity, the potency of an antibiotic, expressed as the minimum inhibitory concentration (MIC), is a measurement of its ability to kill or inhibit growth of bacteria in vitro. Essentially, it is the lowest concentration at which the drug inhibits growth of the bacteria. The lower the MICs, the more potent the antibiotic. MIC is commonly expressed in concentrations of μg/mL.

- ***Susceptibility:*** Connecting the potency of an antibiotic to its clinical utility in the hospital setting can be referred to in terms of susceptibility or non-susceptibility. A susceptible MIC value denotes that an antibiotic can be used as therapy for a particular infection, whereas a non-susceptible MIC value, based on in vitro testing, means the antibiotic should not be used as treatment of the infection because the agent is unlikely to be effective against the causative organism. The common differentiation between susceptibility and non-susceptibility for pathogens is a MIC value of less than or greater than 4 μg/mL, respectively.

- ***Resistance:*** The ability of a pathogen to withstand the activity of an antibiotic that is normally used to treat the organism is known as resistance; the activity of the antibiotic may be compromised, reduced, or lost. Antimicrobial drug resistance can occur as a result of selective pressure, genetic mutation, changes in gene expression, gene transfer, or inappropriate drug use. Examples of resistant mechanisms incorporated by bacteria include: 1) enzymatic deactivation of antibiotics, 2) decreased cell wall permeability, and 3) efflux mechanisms to remove the antibiotics. On occasion, antibiotic-resistance mechanisms can transfer between bacterial species, as observed in CRE where bacteria are able to transfer their resistance to other bacteria within their family.

Resistant Infections

According to the CDC, at least 2 million Americans acquire serious infections with bacteria that are resistant to one or more of the antibiotics specifically designed to treat those particular infections; it is estimated that over 20,000 patients die annually from such resistant infections. In EU, it is estimated that approximately 2.5 million hospital days and 25,000 deaths are related to resistant bacterial infections. The CDC estimates that in the United States, the excess annual cost resulting from these infections is approaching $20 billion.

ESKAPE Pathogens and MDROs

In 2009, the Infectious Diseases Society of America (IDSA) issued a call to action to the medical community in hopes of raising awareness regarding drug-resistant infections and the scant development pipeline of novel therapeutics to treat these infections. The society focused its attention on a group of Gram-positive and Gram-negative bacteria that cause the lion's share of nosocomial (originating in a hospital) infections but are increasingly resistant to many antibiotic agents. Several key MDR organisms (MDROs) are also identified by the CDC using the acronym ESKAPE pathogens. We summarize both the specific ESKAPE pathogens as well as common MDROs in exhibit 11. These pathogens are associated with significant mortality, as the increase in antibiotic resistance has limited the number of effective treatment options.

Exhibit 11
ESKAPE Pathogens and Common Multi-Drug-Resistant Organisms (MDROs)

		CRE Pathogen
ESKAPE Pathogens		
E*nterococcus faecium*	Gram-positive	No
S*taphylococcus aureus*	Gram-positive	No
K*lebsiella pneumoniae*	Gram-negative	Yes
A*cinetobacter baumanii*	Gram-negative	No
P*seudomonas aeruginosa*	Gram-negative	No
Enterobacter species	Gram-negative	Yes
Common Multi-Drug-Resistant Organisms (MDROs)		
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Gram-positive	No
Vancomycin-intermediate *Staphylococcus aureus* (VISA)	Gram-positive	No
Vancomycin-resistant *Staphylococus aureus* (VRSA)	Gram-positive	No
Vancomycin-resistant *enterococcus* (VRE)	Gram-positive	No
Extended-spectrum β-lactamase (ESBLs) producing bacteria	Gram-negative	No
Fluoroquinolone-resistant *Pseudomonas aeruginosa*	Gram-negative	No
Klebsiella pneumoniae carbapenemase (KPC)	Gram-negative	Yes

Sources: Infectious Diseases Society of America (IDSA), and William Blair & Company, L.L.C.

Understanding CRE

CRE refers to a family of bacteria, Enterobacteriaceae, that are difficult to treat because they have high levels of resistance to antibiotics, in particular carbapenems. Multiple ESKAPE pathogens are associated with CRE, including Klebsiella pneumonia and Enterobacter species. We outline details related to carbapenem, resistance mechanisms associated with CRE, and current treatments for CRE below.

Background on Carbapenems

Carbapenems are β-lactam antibiotics similar to penicillins and cephalosporins. Compared with other antibiotic classes, they offer the broadest spectrum of activity, providing coverage of many Gram-negative and Gram-positive bacteria. Similar to other β-lactam antibiotics, carbapenems bind to the penicillin-binding proteins (PBPs), which results in the inhibition of cell well synthesis. In general, carbapenems are less resistant than other β-lactams and are typically considered one of the last lines of therapy for MDR Gram-negative bacterial infections, especially nosocomial pathogens. Besides CRE, other pathogens not covered by carbapenems include MRSA, VRE, and C. difficile.

Resistance Mechanisms to Carbapenems: Serine Carbapenemases and MBL

As with other β-lactam antibiotics, the main mechanism of resistance to carbapenems is by enzymatic hydrolysis of the β-lactam ring through lactamase enzymes. Usually secreted by Gram-negative pathogens, these enzymes break the drug's structure, deactivating its antibacterial properties. Two main types of lactamase enzymes associated with CRE include serine carbapenemases and metallo-β-lactamases (MBLs).

Subtypes of serine carbapenemases. Several subtypes of serine carbapenemases have been identified, including Klebsiella pneumoniae carbapenemase (KPC) and oxacillinase (OXA). First observed in the United States in 2001, KPC is the most-common carbapenemase; the enzyme is encoded by a highly transmissible gene that has spread widely throughout the United States and around the world. The OXA group of β-lactamases typically occurs in Acinetobacter species and is often augmented by clinical isolates through additional resistance mechanisms including efflux.

Subtypes of metallo-β-lactamases. Several varieties of MBLs exist, including imipenem metallo-β-lactamase (IMP), Verona integrin-encoded metallo-β-lactamase (VIM), and the New Delhi metallo-β-lactamases (NDM-1). Originally described in New Delhi, India, in 2009, NDM-1 was first identified in the United States in 2009. Since 2009, only 96 cases have been reported in the United States. Plazomicin and other aminoglycosides display very poor activity against NDM-1 isolates because of their resistance mechanism and the co-expression of an aminoglycoside resistance mechanism, known as ribosomal methyltransferase.

Current Treatments of CRE Are Inadequate With High Mortality Rates

Few treatment options currently exist for CRE. To date, only polymyxins, Tygacil, and some aminoglycosides have been shown to retain in vitro activity against CRE isolates, and as a result have become the only available options for the treatment of CRE. Clinical data supporting the use of carbapenem therapy, either in combination regimens, high-dose prolonged infusion, or via double-carbapenem therapy, remain limited. We discuss the current treatment regimens for CRE below.

Colistin: Limited by nephrotoxicity and growing resistance. Colistin, or polymyxin E, is a member of the polymyxin class of antibiotics, which possess targeted Gram-negative activity. Colistin is polycationic, containing both hydrophilic and lipophilic moieties. Interactions between colistin and the bacterial outer membrane lead to a change in permeability in the cell envelope, which results in a leakage of cellular contents and ultimately to cell lysis, or death. Colistin was originally approved in the 1950s, but because of concerns about nephrotoxicity and neurotoxicity, it was abandoned for more-favorable classes such as aminoglycosides. The incidence of these adverse events remains a concern, and total daily dose and longer duration of treatment are associated with increased risk

of renal dysfunction. Despite its adverse-event profile, colistin is considered to be the first line of therapy for CRE. Recent data suggest that resistance to colistin is emerging, and outbreaks of colistin-resistant CRE have been reported; the all-cause mortality of patients infected with KPC treated with colistin is about 46%.

Tygacil: Considered last resort after meta-analyses indicating increased mortality risk in the primary indicated population. Tygacil, or tigecycline, is a glycylcycline antibiotic belonging to the tetracycline class of antibiotics and possessing good activity against both Gram-negative and Gram-positive bacteria. Tygacil was specifically developed to overcome two major mechanisms of tetracycline resistance, namely tetracycline efflux and ribosomal protection. Similar to tetracycline, Tygacil binds the 30S subunit of the ribosome, which leads to the inhibition of protein synthesis. In the United States, Tygacil, marketed by Pfizer, is approved by the FDA for the treatment of acute bacterial skin and skin structure infection (ABSSSI), complicated intra-abdominal infections (cIAIs), and community-acquired pneumonia (CAP); a major concern regarding Tygacil is the recent meta-analyses of clinical studies that have shown a higher mortality rates in patients treated with Tygacil versus comparator treatments.

For CRE infections, similar to colistin, the all-cause mortality of patients infected with KPC treated with Tygacil is approximately 47%.

Aminoglycosides: Co-expression of aminoglycoside resistant mechanisms in CRE presents an obstacle for current commercially available aminoglycosides. Aminoglycosides inhibit protein synthesis by binding to the 30S ribosomal subunit. Aminoglycosides are primarily used for the treatment of Gram-negative bacteria, and relative to other classes of antibiotics, aminoglycosides have proved fairly stable against the development of resistance. The main mechanisms of resistance to aminoglycosides include: 1) aminoglycoside modifying enzymes (AMEs); 2) mutations to the ribosomal binding site; and 3) decreased cell permeability. Currently available aminoglycosides, including gentamicin, amikacin, and tobramycin, have demonstrated in vitro activity to CRE isolates, but to varying degrees; poor-activity in CRE isolates may be attributed to co-expression of aminoglycoside resistant mechanisms, namely AMEs, which plazomicin was designed to overcome. We note that the all-cause mortality of patients infected with KPC treated with aminoglycosides is about 38%. Major adverse effects of aminoglycosides are nephrotoxicity (renal toxicity) and ototoxicity (damage to the inner ear); nephrotoxicity related to aminoglycoside use is reversible, but ototoxicity is often irreversible.

Combination therapy: Limited improvement over monotherapy. The role of combination therapy is continuing to be defined in the treatment of CRE. The most frequently used combination regimen is colistin+Tygacil; however, colistin+gentamcin and Tygacil+gentamicin are also used in the treatment of CRE. Combinations pairing the carbapenem, meropenem, with colistin, Tygacil or gentamicin, have also been evaluated in the treatment of CRE. All-cause mortality rates for these various double combinations range from approximately 30% (colistin+Tygacil) to 50%. Interestingly, we note that one recent study (Tumbarello et al., *Clin Infect Dis,* 2012) reported the triple combination of colistin, Tygacil, and meropenem led to an all-cause mortality rate of 13% (n=14) in patients with BSIs due to KPC, although the number of patients in this study is very small.

Exhibit 12
Current CRE Therapies and All-Cause Mortality

Regimen	All-Cause Mortality Rates in KPC BSIs	Key Limitations
Colistin	46%	Nephrotoxic, target attainment difficult, growing resistance
Tygacil (tigecycline)	47%	Bacteriostatic, increased risk of death in meta-analysis rendering it the last resort in many indiations
Aminoglycosides	38%	Nephrotoxic, ototoxic, inactivity due to co-expression of aminoglycoside resistance mechanisms
Combination	30-50%	Limited improvement over monotherapies; added toxicity

Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

Plazomicin Is the Most Potent Agent Against CRE

Plazomicin Demonstrates the Highest In Vitro Potency Among Existing Agents

In vitro studies investigating the effectiveness of plazomicin and commercially available antibiotics against Enterobacteriaceae resistant to carbapenems suggest plazomicin may be the most effective therapy. Exhibit 13 presents the minimum inhibitory concentrations (MIC), or the lowest concentration of a specific antibiotic that will inhibit the growth of CRE isolates. Specifically, MIC_{90} and MIC_{50} are defined as the lowest concentration of the antibiotic at which 90% and 50% of the isolates were inhibited, respectively.

Exhibit 13
Potency of Plazomicin and Available Therapies Versus CRE Isolates

Compound	Class	N	MIC50 (µg/ml)	MIC90 (µg/ml)
Plazomicin	**Aminoglycoside**	**807**	**0.5**	**2**
Gentamicin	Aminoglycoside	807	4	128
Amikacin	Aminoglycoside	806	32	64
Ciprofloxacin	Fluoroquinolone	767	8	8
Ceftazidime	Cephalosporin	510	64	>128
Piperacillin/tazobactam	Penicillin/β-Lactamase inhibitor	731	>128	>128
Tygacil (tigecycline)	Glycycline	723	1	2
Colistin (polymyxin B)	Polymyxin	692	1	4

Dark gray boxes=Nonsusceptible; light gray boxes=Susceptible
N=number of strains within the overall set of 807 strains tested vs. the given antibiotic.
Sources: Achaogen, Inc., and William Blair & Company, L.L.C.

Results from the in vitro study were categorized into two groups, susceptible (light gray in the exhibit) and nonsusceptible (dark gray). At the MIC_{90}, all commercial therapies were nonsusceptible. Although plazomicin has yet to be assigned a susceptibility designation, these studies suggest that 96% of CRE isolates were inhibited by plazomicin at a concentration of 2 µg/mL or less, potentially making plazomicin the best therapy against CRE infection.

Plazomicin Overcomes Most Carbapenem Resistance Mechanisms

We summarize the most-common resistance mechanisms to carbapenem and their susceptibility to plazomicin in exhibit 14. Except for NDM-1, plazomicin is effective against the major resistance mechanisms to carbapenem.

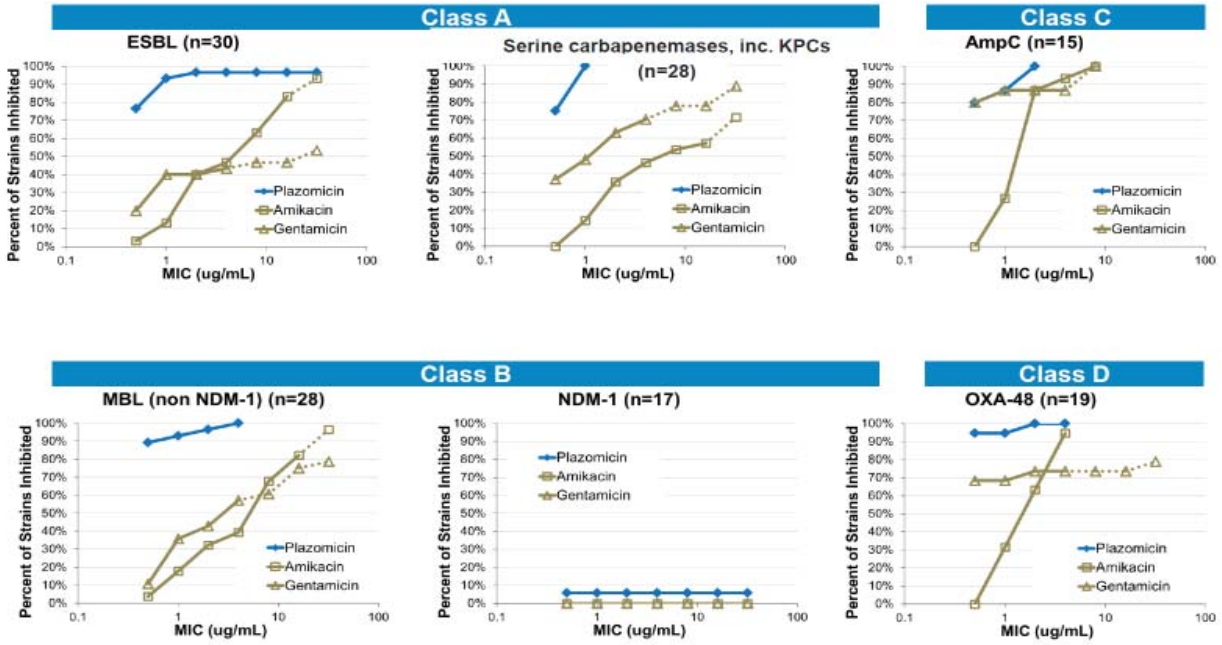
Exhibit 14
Carbapenem Resistance Mechanisms and Plazomicin Activity Against Them

	Susceptibility to Plazomicin
Serine carbapenemases	
Klebsiella pneumoniae carbapenemase (KPC)	≥ 90% @ 1 ug/mL
Oxacillinase (OXA)	≥ 90% @ 1 ug/mL
Metallo-β-lactamases (MBL)	
Imipenem metallo-β-lactamase (IMP)	≥ 90% @ 1 ug/mL
Verona integrin-encoded metallo-β-lactamase (VIM)	≥ 90% @ 1 ug/mL
New Delhi metallo-β-lactamases (NDM-1)	< 10% @ 1 ug/mL

Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

In exhibit 15, on the following page, plazomicin is compared with two other aminoglycosides, amikacin and gentamicin, commonly used against carbapenem-resistant isolates of Enterobacteriaceae. The following carbapenemases were compared: serine carbapenemase, oxacillinase, metallo-β-lactamase (MBL), NDM-1, extended-spectrum β-lactamases (ESBL), and AmpC β-lactamases. Plazomicin was more effective than either amikacin or gentamicin against isolates with serine carbapenemase, oxacillinase, and MBL activity. We note that plazomicin retained 90% or more activity against isolates at a MIC of less than or equal to 1 µg/mL. However, against isolates with NDM-1 activity, plazomicin was no different from amikacin or gentamicin. We note that NDM-1 isolates typically co-express ribosomal methyltransferase, an enzyme that renders plazomicin and other aminoglycosides ineffective.

Exhibit 15
Achaogen, Inc.
Potency of Plazomicin Against Enterobacteriaceae Strains

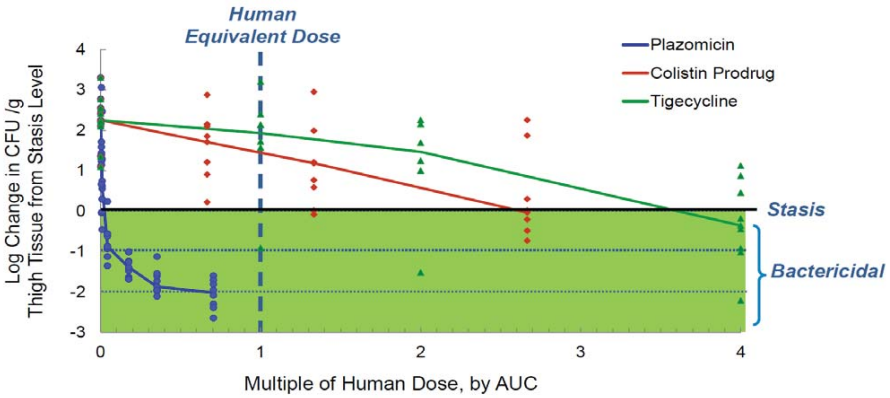


Source: Achaogen, Inc.

In Vivo Studies Demonstrate Plazomicin's Superior Activity Over Colistin and Tigecycline

In different mouse models of bacterial infection, a known amount of CRE was injected into the thigh muscle or lung of the animals. After two hours, animals were treated with plazomicin, colistin, or tigecycline for one day. Exhibit 16 shows the results of the various treatments against eight CRE strains in a mouse thigh infection model. Plazomicin reduced the amount of bacteria by up to 100 times compared with colistin and tigecycline, which displayed poor efficacy. This finding is consistent with the high mortality associated with colistin- and tigecycline-treated patients with CRE infections. With much improved PK and cidality, plazomicin could prove to be superior in the clinic to colistin and tigecycline, which is the aim of the ongoing Phase III CARE study.

Exhibit 16
Achaogen, Inc.
Plazomicin Versus Colistin and Tigecycline in CRE Infected Mouse *



* CRE clinical isolates, N=9

Source: Louie et al. ECCMID 2013, Poster # LB 2961, and Achaogen, Inc.

We note that although in vitro studies demonstrate that plazomicin's MICs against CRE may be only incrementally better than current standard of care colistin and tigecycline, in vivo models demonstrate a decidedly unique and superior plazomicin profile: rapidly cidal at clinically relevant doses. Colistin and tigecycline were cidal at levels greater than two times the clinically relevant doses. This clear pharmacokinetic advantage and rapid cidal activity are key for the potential success of the ongoing Phase III study.

In summary, we believe that such a profile for plazomicin represents the best among existing regimens and agents against CRE.

In Vitro Studies Support Phase III Dosing Combination
Plazomicin has been studied in combination with meropenem and tigecycline in vitro. The combination did not reduce the clinical activity of plazomicin in eight CRE isolates, further supporting the use of the combinations. We note that the combination strategy is being employed in the current Phase III study.

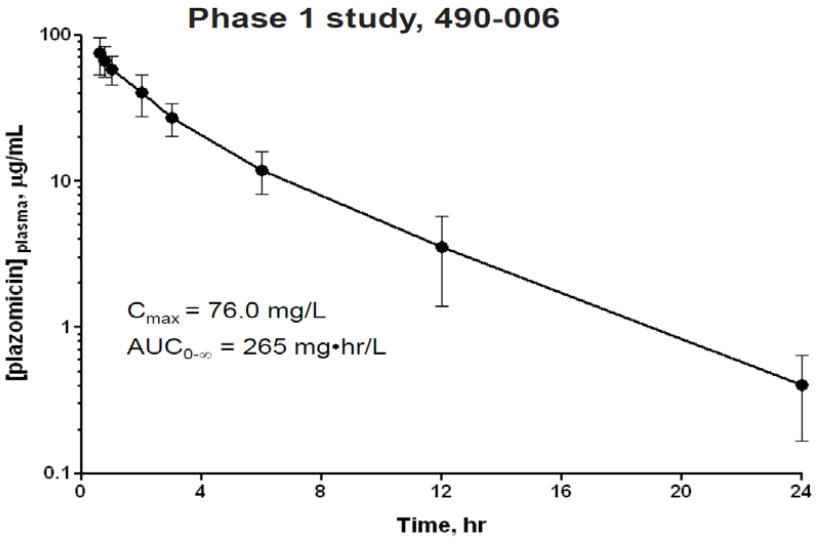
Plazomicin Clinical Program

Phase I: First in Human Studies

Phase I demonstrates good safety and tolerability; pharmacokinetic (PK) data are linear but renal excretion may require dose adjustments. Plazomicin demonstrates good tolerability and safety when dosed up to 20 mg/kg in a single dose or multiple doses of up to 15 mg/kg. Adverse events were mild to moderate in nature, consisting of headache, numbness or tingling, dizziness, nausea, and drowsiness. In a second Phase I study, the initial dose was 15 mg/kg of plazomicin infused over 10 minutes. This dosing resulted in a moderate, transient hypotension, which was alleviated by increasing infusion time to 30 minutes.

Data from the PK study demonstrated dose proportionality and linearity in plasma. Notably, drug concentrations in lung epithelial lining fluid were similar to those previously reported by amikacin, another aminoglycoside antibiotic. With respect to drug metabolism, plazomicin is renally excreted, and Phase I studies confirmed significant PK alterations in those with altered renal function, thus requiring a dose adjustment. In the Phase III study, a companion diagnostic is employed to measure plasma plazomicin as an additional step to ensure optimal dosing. We illustrate plazomicin's pharmacokinetic profile in exhibit 17, on the following page.

Exhibit 17
Achaogen, Inc.
Plazomicin PK Profile From Phase I Study



Source: Achaogen, Inc.

Phase II Study: Establishing Activity and Safety, Albeit in cUTIs

Design and inclusion criteria. The randomized, double-blind, 145-patient Phase II study evaluated the efficacy of plazomicin versus levofloxacin in patients with complicated urinary tract infections (cUTIs), including acute pyelonephritis. In the first part of the study, patients were randomized in a 1:1:1 fashion receiving 10 mg/kg plazomicin, 15 mg/kg plazomicin, or 750 mg levofloxacin administered once daily for five days. In the second part of the study, patients were randomized in a 2:1 fashion to either to 15 mg/kg plazomicin or 750 mg levofloxacin.

The primary efficacy endpoint was the proportion of patients who achieved microbiological eradication at the test-of-cure visit (day 12). Microbiological eradication was assessed in two populations: 1) modified intent-to-treat (MITT)—those with at least one causative pathogen isolated from an acceptable urine specimen before treatment, and 2) a microbiologically evaluable (ME) population—a smaller subset of the MITT population that included patients who received study treatment for a pre-specified duration and had an acceptable urine specimen at test of cure. The secondary efficacy endpoint of the trial was clinical outcome.

Efficacy results suggest no difference among treatment groups. Across both groups, MITT and ME, there were no significant differences in responses between plazomicin and levofloxacin. In the MITT group, response rates for plazomicin and levofloxacin were 58.7% versus 58.6%, respectively. For the ME group, plazomicin and levofloxacin demonstrated responses of 88.1% and 81.0%, respectively.

Exhibit 18
Achaogen, Inc.
Phase II cUTI Efficacy

By Patient Microbiological Response	Plazomicin 10 mg/kg	Plazomicin 15 mg/kg	Levofloxacin 750 mg
Microbiologically Evaluable (ME)			
No. of patients	7	35	21
Eradication, n (%)	6 (85.7%)	31 (88.6%)	17 (81.0%)
95% Confidence Interval	42.1%–99.6%	73.3%–96.8%	58.1%–94.6%
Difference (95% CI)			−7.6% (−31.3%, 16.0%)
Modified Intent-to-Treat (MITT)			
No. of patients	12	51	29
Eradication, n (%)	6 (50.0%)	31 (60.8%)	17 (58.6%)
95% CI	21.1%–78.9%	46.1%–74.2%	38.9%–76.5%
Difference (95% CI)			−2.2% (−27.2%, 22.9%)

Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

Plazomicin is relatively safe with a similar profile to levofloxacin; plazomicin is associated with a slight increased risk for nephrotoxicity and ototoxicity. With respect to safety, adverse events rates were similar between plazomicin and levofloxacin. There were no drug-related serious adverse events in the plazomicin arm. In terms of nephrotoxicity, minor changes in serum creatinine occurred in 5.2% plazomicin-treated patients versus 4.5% levofloxacin-treated patients. We highlight this because plazomicin is cleared through the kidneys. Lastly, hearing and balance of patients were closely assessed, as aminoglycosides are known to be associated with ototoxicity. In the plazomicin arm, there was one case of mild transient vertigo and a mild unilateral tinnitus that persisted and was considered permanent. Neither patient tested positive for changes in hearing function or balance.

Exhibit 19
Achaogen, Inc.
Phase II cUTI Safety

Preferred Term, n (%)	Plazomicin 10 mg/kg (N=22)	Plazomicin 15mg/kg (N=74)	Levofloxacin 750 mg/kg (N=44)
Patients With Any Adverse Event	7 (31.8)	26 (35.1)	21 (47.7)
Headache	2 (9.1)	6 (8.1)	3 (6.8)
Diarrhea	0 (0.0)	4 (5.4)	2 (4.5)
Dizziness	0 (0.0)	4 (5.4)	0 (0.0)
Nausea	0 (0.0)	4 (5.4)	0 (0.0)
Vomiting	0 (0.0)	4 (5.4)	1 (2.3)
Dysgeusia	0 (0.0)	0 (0.0)	2 (4.5)
Gastritis	1 (4.5)	2 (2.7)	0 (0.0)
Hypokalaemia	0 (0.0)	1 (1.4)	2 (4.5)
Pruritus	1 (4.5)	0 (0.0)	2 (4.5)
Upper Respiratory Tract Infection	0 (0.0)	0 (0.0)	2 (4.5)

Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

We summarize all completed Phase I and Phase II studies for plazomicin in exhibit 20.

Exhibit 20
Achaogen, Inc.
Completed Plazomicin Studies

Trial	Objectives	Design	Plazomicin Doses	No. of Subjects
		Phase I PK, Safety, and Tolerability		
490-001	Safety and PK after single and multiple doses in healthy subjects	Double-blind, randomized, placebo-controlled, parallel-group, dose-escalation study	1, 4, 7, 11, 15 mg/kg IV for 3−10 days	39
490-003	Safety, PK, and lung penetration in healthy subjects	Double-blind, randomized, placebo-controlled	Cohort 1: 15 mg/kg IV for 5 days Cohort 2A / 2B: 10.7/15 mg/kg IV, single dose	40
490-004	Safety and PK in subjects with renal impairment	Open label	7.5 mg/kg IV, single dose	24
490-006	Thorough QT or TQT in healthy subjects	Randomized, double-blind, controlled crossover	15 mg/kg IV, single dose 20 mg/kg IV, single dose	Part 1=8 Part 2=56
		Phase II Efficacy and Safety		
490-002	Safety, efficacy, and PK in patients with cUTI	Double-blind, randomized, comparator-controlled, multicenter	10 mg/kg IV for 5 days 15 mg/kg IV for 5 days	145

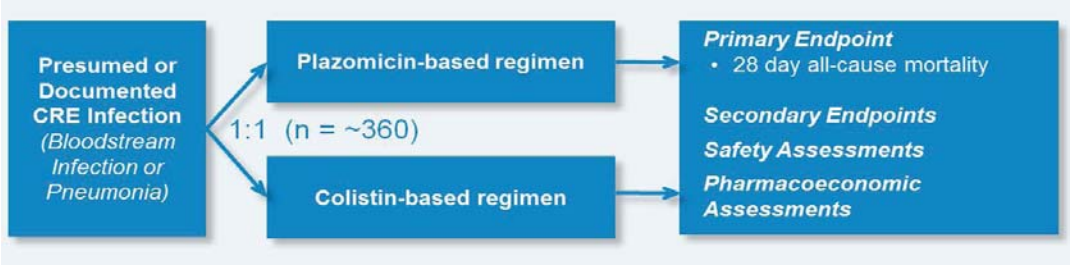
Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

Phase III Program

Background on Phase III CARE study. The 360-patient Phase III study, named CARE (Combating Antibiotic-Resistant Enterobacteriaceae), is a randomized, open-label study comparing efficacy and safety of plazomicin against colistin in patients with bloodstream infections (BSIs) or hospital-acquired pneumonia resulting from CRE. Patients who are infected with either presumed or confirmed pathogen that exhibit MIC of 4 µg/mL or greater against the broadest spectrum carbapenems will be enrolled and randomized in a 1:1 fashion to either the plazomicin- or colistin-based regimen. Patients are allowed one adjunctive antibiotic, either tigecycline or meropenem, at the time of randomization, at the discretion of the investigator. The treatment duration is 7 to 14 days. All-cause mortality, the primary endpoint, will be assessed at day 28, and late safety follow up is planned at day 60 (exhibit 21). The study was initiated in first quarter 2014, with top-line data expected in the first half of 2017.

Secondary endpoints include time to death, microbiological and clinical responses, resolution of fever, improvement in oxygenation for pneumonia patients, safety, and pharmacoeconomic assessments.

Exhibit 21
Achaogen, Inc.
Plazomicin Phase III Design



Source: Achaogen, Inc.

Dosage and use of a companion diagnostic to ensure optimal dosing and highest cidality. Plazomicin treated patients will receive an initial 30-minute IV dose of up to 15 mg/kg. Initial dosing and interval dosing will be determined by a baseline renal function test. Further dosing will be optimized for each patient based on renal function and the in vitro assay (see the appendix).

Phase III plazomicin dosing is based on pharmacokinetic/pharmacodynamics (PK/PD) modeling, using preclinical animal studies and Phase I/II clinical data. Based on this model, it is predicted that 92% of patients should have sufficient plazomicin levels in the blood and in the lungs to combat CRE infections. The target plazomicin plasma concentration is about 2-3 times higher than MIC levels.

Phase III dosing will be optimized for each individual through a therapeutic drug management assay co-developed with ARK Diagnostics. This is a necessary component of the study given that plazomicin is a renally excreted drug and may require dose alterations based on changes in renal function. The assay is not yet approved by the FDA, but the company received an investigational device exemption approval from the FDA for use in the Phase III study. As a result, plazomicin's success is partly dependent on the full approval of the in vitro assay.

Colistin will be administered intravenously in two stages: 1) an initial dose of 5 mg/kg and 2) a maintenance dose of 5 mg/kg every 8 or 12 hours for up to 14 days. Similar to plazomicin, colistin dosing will be adjusted depending on renal function.

Key inclusion exclusion criteria. Given the primary endpoint of all-cause mortality, the study looks to enroll patients who will most likely demonstrate a survival benefit when treated with a more efficacious regimen. As a result, enrolled patients will have received less than 72 hours of empirical therapy and have either confirmed or presumed CRE infection. Excluded patients are those with colistin-resistant infections, refractory septic shock, or those who require more than 14 days of antibiotic therapy. To better assess mortality in terms of disease severity, all patients will be evaluated using the APACHE II score, which ranges from 0 to 71, with 71 being most severe. Enrolled patients will have APACHE II scores ranging from 15 to 30. Patients will be stratified by APACHE II scores, infection type (bloodstream or pneumonia), and time from the initiation of empirical therapy.

Two interim analyses planned in CARE. There are two unblinded interim analyses of efficacy and futility built into the study. The two interim analyses are to occur when 33% and 67% of patients have reached day 28 (the end of the study), which is projected to occur in the end of 2015 and the end of 2016, respectively.

Phase III statistical assumptions are based on a meta-analysis. Literature on mortality rates of serious CRE infections is limited. A meta-analysis of three observational studies describing the outcome of 309 patients with BSIs infected with carbapenemase-producing Enterobacteriaceae formed the basis of the statistical assumptions for the Phase III CARE study.

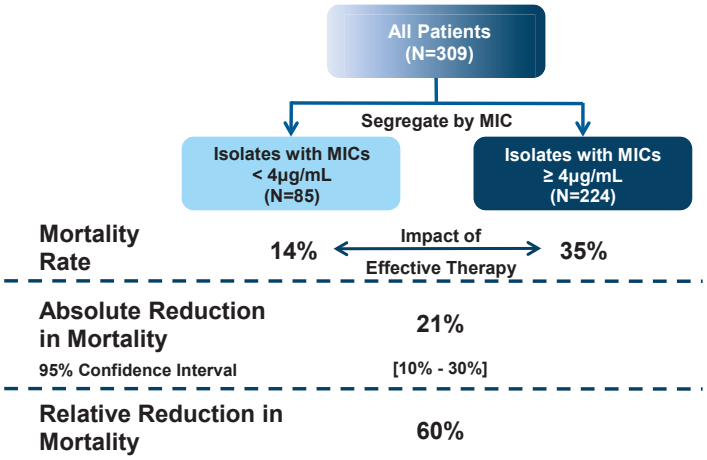
In the meta-analysis (exhibit 22a), for patients who were infected by CRE (carbapenem MIC of over 4 mg/ml), the all-cause mortality was as high as 35%. In contrast, for patients who were infected by bacteria still sensitive to carbapenems (carbapenem MIC of less than 4 mg/ml), the mortality rate is reduced to 14%, representing a relative reduction of 60% and an absolute reduction of 21%.

In the CARE study (exhibit 22b), only patients who are infected with CRE (carbapenem MICs greater than 4 mg/ml) are enrolled. As discussed previously, plazomicin demonstrated strong cidal activity against MDR Enterobacteriaceae, including CRE with various carbapenem-resistant mechanisms. Therefore majority of the CREs should remain sensitive to plazomicin (equivalent to MIC less than 4 mg/ml); as a result, the plazomicin-treated group should have a mortality rate approach the 14%

in the meta-analysis. In the comparator arm in CARE, colistin has demonstrated limited activity against CRE (equivalent to MIC great than 4 mg/ml), and the mortality rate in that group should approach the 35% as observed in the meta-analysis.

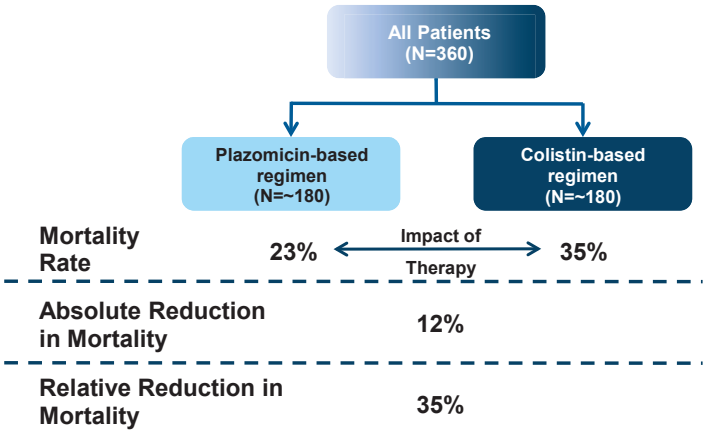
Exhibit 22
Achaogen, Inc.
Meta-Analysis and Assumptions for Phase III Study

a) Meta-Analysis of Mortality in Patients With CPE Blood Infection



Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

b) Assumptions for Phase III Study in Patients With Presumed or Confirmed CRE Infections



Sources: Achaogen, Inc. and William Blair & Company, L.L.C.

The Phase III CARE study is powered at 70% to detect a relative reduction of 35% absolute reduction of 12% in all-cause mortality. The CARE study is powered at 70% to detect the 35% relative reduction and 12% absolute reduction (from 35% assumed for the colistin arm to 23% for the plazomicin arm) in all-cause mortality, as compared with the 60% relative and 21% absolute reduction observed in the meta-analysis, leaving a margin of safety (exhibit 22).

Handicapping the probability of success of CARE: we estimate 70%. While we believe plazomicin is a viable antibiotic, the bulk of the questions concern trial design and endpoints.

- *The potency of plazomicin in CRE is based on in vivo and in vitro studies, as discussed above; translation to humans is predicted but needs to be demonstrated.* While plazomicin is comparable to levofloxacin for safety and efficacy in cUTIs, there are no prior dedicated studies investigating the effects of plazomicin in CRE. Although we are relatively confident that efficacy of antibacterials generally translates from in vivo models to the clinic, it still needs to be demonstrated in this case. We note that Achaogen will initiate a supporting single-arm Phase II study in CRE in late 2014 and data should read out in late 2015. This study should provide the first data on plazomicin's activity in CRE and if successful should create heightened excitement and confidence in the ongoing Phase III CARE study.

- *Phase III enrollment is projected to take three years, but the emerging epidemiology is a moving target.* While the study projected to take three years, the exact timeline is difficult to predict, as enrollment is dependent on the occurrence of a rare disease and patient enrollment may not be constant. On one hand, increasing CRE incidence may speed up the projected timeline. On the other hand, enrollment may also be dampened by competitors who have their own studies in progress.

- *The statistical assumptions for the Phase III study are based on a meta-analysis of three observational studies.* There is limited data in literature on mortality rates from CRE and as discussed in detail herein, the Phase III study is based on a meta-analysis describing mortality outcomes from 309 patients infected with carbapenemase-producing Enterobacteriaceae. The meta-analysis classified outcomes of these patients into two groups: resistant or sensitive to carbapenems, and observed that the absolute mortality difference between the two groups was 21% (60% relative difference). Based on such data, the underlying assumption for the CARE study is that plazomicin treatment should afford patients a similar mortality benefit to those in the sensitive group in the meta-analysis, which is a 21% absolute mortality reduction from the current standard of care.

- *Although the Phase III study is based on a meta-analysis, a margin of safety is built in, increasing the probability of success, in our opinion.* The Phase III study is powered at 70% to detect an absolute reduction in mortality of 12% (35% relative reduction). These assumptions appear conservative as compared with the observed mortality reduction of 21% (60% relative reduction) demonstrated by the meta-analysis. This difference allows for a reasonable margin of safety, thus increasing the probability of success, in our opinion.

- *Interim analyses are built in to provide a potential opportunity to adjust sample size if necessary, ensuring power of the study.* There will be two unblinded interim analyses occurring when 33% and 67% of the patients in the study have reached day 28 (the end of the study). A data monitoring committee will review the data and determine if the study should be stopped based on efficacy or futility. These interim analyses might also help determine whether more patients will need to be enrolled to ensure power of the study.

- *A companion diagnostic will be employed to ensure plazomicin plasma and lung concentration reaches bactericidal levels, thereby ensuring maximum efficacy in every patient.* Since plazomicin is renally excreted, dosing will be individually optimized using a diagnostic to ensure sufficient

drug plasma and lung concentration to combat infections. Pharmacometric modeling developed at Achaogen predicts that 92% of patients should be able to achieve sufficient drug levels in the blood or the lung that are effective against their CRE infection.

- *Phase III study is enriched with patients who will most likely see a mortality benefit from plazomicin treatment.* To better assess mortality in terms of disease severity, all patients will be evaluated using the APACHE II score, which ranges from 0 to 71, with 71 being most severe. Enrolled patients will have APACHE II scores ranging from 15 to 30. We highlight this because it ensures that enrolled patients are neither too healthy nor too sick, increasing the odds of demonstrating a mortality benefit.

- *The safety profile while tested is still unknown when used for a longer duration of treatment in a sicker patient population.* In the Phase II cUTI study, patients were treated for 5 days, as compared with the expected 7 to 14 days in the Phase III trial. While the Phase II study demonstrated a safe and tolerable profile, there was one case of mild nephrotoxicity and two cases of mild ototoxicity, which may be of concern. Undoubtedly, the risk/benefit profile will be different in this sicker population, with patients and regulators willing to accept greater risk if a significant mortality benefit is demonstrated.

- *High risk, high reward: The primary endpoint of mortality is bold and novel to antibiotics.* We highlight this because the mortality endpoint is unlike the typical antibiotic study. Specifically, the registrational trial will strive for superiority in survival. If such a label is obtained, plazomicin should be preferentially used in the labeled indication

Plazomicin Regulatory Strategy and Outlook

Fast-Track Designation
Achaogen has received fast-track designation from the FDA for the development of plazomicin for the treatment of serious and life-threatening infections. Fast track is one of several approaches incorporated by the FDA in its assessment of novel therapies, which is designed to facilitate the development and expedite the review of medicines to treat serious conditions that fulfill an unmet medical need.

An Special Protocol Assessment (SPA) Is in Place for the Phase III Study CARE
The Phase III CARE study is being conducted under a SPA—a typical strategy to gain FDA concurrence with respect to a Phase III study design, clinical endpoints, and statistical analyses in anticipation of regulatory approval. As CARE is the first pathogen-specific pivotal study with a superiority design in survival, it is important that a SPA is in place and that Achaogen and the FDA are in full agreement on the study design and various requirements for approval.

Two Additional Confirmatory Safety and Efficacy Studies Planned; Additional Patients Will Meet the 300-Person Safety Database Requirement
The Phase II supportive study will be a single-arm, open-label study investigating the effects of plazomicin on CRE infections in 50 patients. The study will provide additional safety and efficacy support based on clinical and microbiological outcomes. The study will begin in late 2014 with top-line data expected in fourth quarter 2015.

The safety study will be a single-arm study enrolling 70 patients to meet the 300-person safety database requirement. The study will begin in 2015, following the first interim analysis in the Phase III study and data is expected during first half 2017.

Data from supportive Phase II efficacy study, expected in fourth quarter 2015, is likely to serve as major catalyst for plazomicin program. Achaogen plans to initiate a 50-patient, single-arm Phase II supportive study during fourth quarter 2014 and report data by year-end 2015. The study will assess clinical and microbiological endpoints, but not survival endpoints.

We believe the goals of the study are a few fold: 1) the 50 patients will constitute part of plazomicin's overall safety database; 2) the study plans to enroll a broader CRE patient population, including patients with cUTI, cIAI (complicated intra-abdominal infections) and colistin-resistant infections in addition to the BSI and pneumonia eligible for the Phase III study, so as to gain broader experience of plazomicin in various CRE infections; 3) successful data in late 2015 could generate excitement, boost confidence and help accelerate enrollment in the Phase III CARE study; and 4) successful data could also serve as potential supportive data should Achaogen request Breakthrough Therapy designation for plazomicin for the treatment of CRE.

As a result, we believe results from the Phase II supportive study are a significant catalyst for the plazomicin program in late 2015.

Composition of Plazomicin's Registration Package; Approval Second Half 2018
As discussed above, the full plazomicin registration package includes the Phase III CARE study, the Phase II supportive study, as well as a third study focused on safety. We anticipate regulatory submissions by year-end 2017, resulting in a potential approval of plazomicin by second half 2018. On the efficacy side, a successful CARE study with data from the supportive Phase II study is sufficient for approval. On the safety side, the CARE study, in conjunction with the 50-person supportive efficacy Phase II study (expected in fourth quarter 2015) and a 70-person safety study (expected in first half of 2017), should allow Achaogen to meet the 300-person safety database requirement for approval.

Competitive Landscape for Plazomicin

Several regimens in Phase III development for Gram-negative pathogens might potentially compete with plazomicin. The majority of regimens fall under two combination categories, either 1) cephalosporin/β-lactamase inhibitor combos or 2) carbapenem/β-lactamase inhibitor combos. The novel β-lactamase inhibitors incorporated in the combination regimens, including avibactam, MK-7655 and RPX7009, have activity against carbapenemases and are designed to restore the activity of their paired antibiotics against the carbopenemase-producing bacteria. Another competitor is the novel fluorocycline eravacycline (TP-434) from Tetraphase Pharmaceuticals.

Only one competitive regimen, Carbavance from the Medicines Company, is expected to enter Phase III development in 2014 for the treatment of MDR Gram-negative pathogens including CRE; the Medicines Company gained rights to Carbavance following its acquisition of Rempex Pharmaceuticals in December 2013.

In exhibit 23, on the following page, we list the current Phase III competitive landscape for Gram-negative pathogens, including their ability to treat specific CRE pathogens.

Exhibit 23
Plazomicin and Competitive Landscape for Phase III Intravenous Antibiotics for Gram-Negative Bacteria, Including CRE

Drug (Combination)	Class	Company	Indication(s)	Activity for Enterobacteriaceae			CRE Focus
				ESBL	sCBP	mCBP	
Plazomicin	**Aminoglycoside**	**Achaogen**	**CRE infections, BSI and HAP/VAP**	**Yes**	**Yes**	**Yes ***	**Yes**
CXA-201 (ceftolozane/tazobactam)	Antipseudomonal cephalosporin/ β-Lactamase inhibitor combination	Cubist	cUTI, cIAI	Yes	No	No	No
CAZ-104 (ceftazidime/avibactam)	Antipseudomonal cephalosporin/ β-Lactamase inhibitor combination	AstraZeneca / Forest	cUTI, cIAI	Yes	Yes	No	No
Imipenem/MK-7655	Carbapenem/ β-Lactamase inhibitor combination	Merck	cUTI, cIAI	Yes	Yes	No	No
Eravacycline	Fluorocycline	Tetraphase	cUTI, cIAI	Yes	Yes	Yes	No
Carbavance (biapenem/RPX7009)	Carbapenem/ β-Lactamase inhibitor combination	Medicines Co.	cUTI, CRE-infections **	Yes	Yes	No	Yes

* Activity in non-New Delhi metallo-beta-lactamase; ** Studies expected to start in 2014
BSI: bloodstream infections; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; cUTI: complicated urinary tract infections;
cIAI: complicated intra-abdominal nfection; ESBL: extended-spectrum β-lactamase (ESBLs) producing bacteria
sCBP: serine carbapenemase producers such as Klebsiella pneumoniae carbapenemase (KPC);
mCBP: metallo-carbapenemase producers such as VIM (Verona integron-encoded metallo-β-lactamase), IMP (Imipenem metallo-β-lactamase), and NDM (New Delhi metallo-beta-lactamase)

Sources: Infectious Diseases Society of America (IDSA), and William Blair & Company, L.L.C.

It is evident from exhibit 23 that plazomicin has the broadest activity against Enterobacteriaceae among the competitive agents and regimens. Further, plazomicin is also the only agent that has a singular focus against CRE, and is pursuing superiority in survival in the Phase III studies. We believe a label of superior survival should establish plazomicin as the standard of care in this setting.

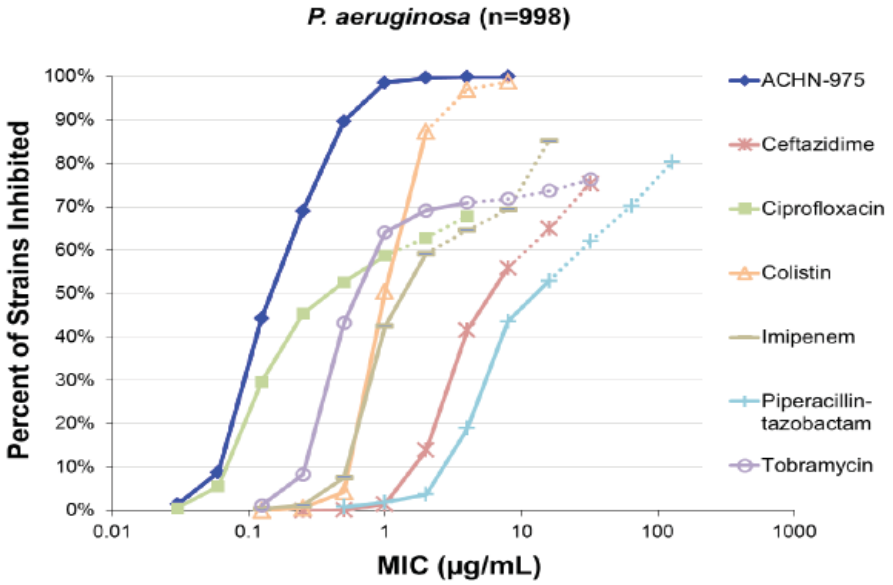
Anti-Pseudomonal Programs

A key area of focus is discovering novel medicines against serious infections caused by MDR Pseudomonas aeruginosa. In 2012, P. aeruginosa accounted for about 20% of the 3 million reported hospital-treated pneumonia cases in the United States, EU, and Japan. Of these, approximately 13% are MDR and associated with high morbidity and mortality rates. Given the mortality and costs associated with these infections, the CDC has declared this a "serious" threat.

LpxC Inhibitors Are a Novel Class of Anti-Pseudomonal Antibiotic
LpxC is an essential enzyme for the outer membrane synthesis in Gram-negative bacteria; Achaogen has focused its efforts on developing compounds to inhibit LpxC. This new class of antibiotics has demonstrated potent in vitro activity against P. aeruginosa. To date, the developed LpxC compounds have demonstrated no cross-resistance with current antibiotics, thus retaining activity against strains harboring resistance mechanisms that inactivate many other marketed antibiotics.

ACHN-975 has the most potent in vitro activity against P. aeruginosa. ACHN-975 is the most-advanced drug candidate and has demonstrated activity against approximately 1,000 P. aeruginosa clinical isolates. Exhibit 24 demonstrates the effectiveness of ACHN-975 versus other antibiotics against P. aeruginosa. The dotted lines begin at the MIC value considered non-susceptible for the particular antibiotic, and only ACHN-975 has a susceptible MIC_{90} among the various agents tested.

Exhibit 24
Achaogen, Inc.
ACHN-975 Potency Against Pseudomonal Clinical Isolates



Source: Achaogen, Inc.

Two Phase I studies conducted but toxicity halts further progress. The first-in-human Phase I study of ACHN-975 given intravenously as single doses demonstrated good tolerability with a linear, dose-dependent PK. The second Phase I study explored multiple doses of ACHN-975; the first three subjects developed inflammation at the infusion site, with venus thrombosis observed in one of the subjects. There were no signs of systemic inflammatory reaction. The company is exploring preclinical models to reproduce this toxicity. If possible, an alternative formulation or pro-drug will be pursued.

Exhibit 25
Achaogen, Inc.
Income Statement
(dollars in thousands)

	2012A	2013A	2014E					2015E
			Q1E	Q2E	Q3E	Q4E	FY:14E	
Revenues								
Plazomicin US revenues	$0	$0	$0	$0	$0	$0	$0	$0
Plazomicin OUS royalties	-	-	-	-	-	-	-	-
Collaboration and licensing revenue	-	-	-	-	-	-	-	-
Contract and grant revenue	17,941	18,512	7,500	7,500	7,500	7,500	30,000	24,000
Total Revenues	**17,941**	**18,512**	**7,500**	**7,500**	**7,500**	**7,500**	**30,000**	**24,000**
Expenses								
COGS	-	-	-	-	-	-	-	-
R&D expense	26,581	23,484	7,500	7,575	7,651	7,727	30,453	31,843
SG&A expense	7,349	6,992	2,500	2,525	2,550	2,576	10,151	10,982
Total Operating Expenses	33,930	30,476	10,000	10,100	10,201	10,303	40,604	42,825
Operating Income	(15,989)	($11,964)	(2,500)	(2,600)	(2,701)	(2,803)	(10,604)	(18,825)
Interest income	51	193	11	81	78	75	244	257
Interest expense, net	(2,427)	(1,341)	(217)	(217)	(217)	(217)	(868)	(231)
Other (expense) income, net			(1,000)	-	-	-	(1,000)	-
Total Other Income (Expense)	(18,365)	(13,112)	(3,706)	(2,736)	(2,840)	(2,945)	(12,228)	(18,799)
Pretax income/(loss)	(18,365)	(13,112)	(3,706)	(2,736)	(2,840)	(2,945)	(12,228)	(18,799)
Other comprehensive gain/(loss)	-	-	-	-	-	-	-	-
Provision for income taxes/(income)	-	-	-	-	-	-	-	-
Net Income/(Loss)	**($18,365)**	**($13,112)**	**($3,706)**	**($2,736)**	**($2,840)**	**($2,945)**	**($12,228)**	**($18,799)**
GAAP EPS		**($1.36)**	**($0.21)**	**($0.15)**	**($0.16)**	**($0.16)**	**($0.69)**	**($1.04)**
Weighted average shares outstanding, diluted		9,673	17,731	17,781	17,831	17,881	17,806	18,068

Sources: Achaogen, Inc. and William Blair & Company, L.L.C. estimates

Exhibit 26
Achaogen, Inc.
Balance Sheet
(dollars in thousands)

	2012A	2013A	2014E					2015E
			Q1E	Q2E	Q3E	Q4E	FY:14E	
Current assets								
Cash and cash equivalents	$7,073	$10,738	$80,822	$77,688	$75,033	$72,274	$72,274	$55,528
Contracts receivable	4,258	7,230	9,730	9,230	8,730	8,230	8,230	7,730
Inventories, net	-	-	-	-	-	-	-	-
Prepaid and other current assets	397	1,873	1,873	1,873	1,873	1,873	1,873	1,873
Deferred financing costs, current portion	-	-	-	-	-	-	-	-
Other current assets	-	-	-	-	-	-	-	-
Total current assets	11,728	19,841	92,425	88,791	85,636	82,377	82,377	65,131
Property and equipment, net of accumulated depreciation	1,344	743	743	743	743	743	743	843
Restricted Cash	127	127	127	127	127	127	127	127
Deferred financing costs, less current portion	-	-	-	-	-	-	-	-
Deposits and Other assets	67	47	47	47	47	47	47	47
Total assets	**13,266**	**20,758**	**93,342**	**89,708**	**86,553**	**83,294**	**83,294**	**66,148**
Current liabilities								
Accounts payable	2,910	2,923	3,173	3,423	3,673	3,923	3,923	4,923
Accrued liabilities	1,567	3,004	3,054	3,554	4,054	4,554	4,554	6,554
Notes payable, current portion	4,536	4,989	4,989	3,875	2,761	1,647	1,647	-
Related-party convertible notes payable	2,687	-	-	-	-	-	-	-
Other current liabilities	334	73	73	73	73	73	73	73
Total current liabilities	12,034	10,989	11,289	10,925	10,561	10,197	10,197	11,550
Deferred rent	69	125	125	125	125	125	125	125
Derivative liability	1,398	-	-	-	-	-	-	-
Related-party convertible loan payable	5,441	-	-	-	-	-	-	-
Notes payable, noncurrent portion	6,311	1,698	584	-	-	-	-	-
Other long-term liabilities	237	244	244	244	244	244	244	244
Total liabilities	25,490	13,056	12,242	11,294	10,930	10,566	10,566	11,919
Stockholders' equity	(112,578)	(124,576)	81,100	78,414	75,623	72,728	72,728	54,229
Convertible preferred stock	100,354	132,278	-	-	-	-	-	-
Total liabilities, convertible preferred and stockholders' equity	**$13,266**	**$20,758**	**$93,342**	**$89,708**	**$86,553**	**$83,294**	**$83,294**	**$66,148**

Sources: Achaogen, Inc. and William Blair & Company, L.L.C. estimates

Exhibit 27
Achaogen, Inc.
Statement of Cash Flows
(dollars in thousands)

	2012A	2013A	2014E	2015E
Net cash from operating activities				
Net Income (Loss)	($18,365)	($13,112)	($12,228)	($18,799)
Adjustments				
Depreciation and amortization	565	506	557	612
Stock-based compensation expense	829	1,053	1,158	1,274
Loss on asset disposition	-	10	-	-
Non-cash interest expense relating to notes payable	524	472	391	104
Non-cash interest expense relating to related-party convertible loan payable	1,246	197	-	-
Non-cash restructuring charges	-	196	-	-
Change in Operating Assets and Liabilities				
Contracts receivable	631	(2,972)	(1,000)	500
Prepaid and other assets	98	(1,456)	-	-
Accounts payable and accrued liabilities	(1,911)	1,450	2,550	3,000
Other liabilities	(379)	(198)	-	-
Net cash used in operating activities	**(16,762)**	**(13,854)**	**(8,572)**	**(13,309)**
Cash flows from investing activities				
Purchase of property and equipment	(568)	(110)	(121)	(133)
Change in restricted cash	35	-	-	-
Purchase of short-term investments	-	-	(25,000)	-
Sales of short-term investments	-	-	-	10,000
Maturities of short-term investments	-	-	-	-
Net cash used in (provided by) investing activities	**(533)**	**(110)**	**(25,121)**	**9,867**
Cash flows from financing activities				
Proceeds from issuance of convertible preferred stock, net of issuance costs	-	22,200	-	-
Proceeds from issuance of related-party convertible notes payable	2,687	-	-	-
Proceeds from the exercise of stock options, net of repurchases	174	61	400	1,200
Proceeds from issuance of related-party convertible loan payable	2,445	-	-	-
Proceeds from issuance of notes payable	7,996	-	-	-
Proceeds from initial public offering, net of offering costs	-	-	77,004	-
Repayment of notes payable	(1,462)	(4,632)	(5,325)	(1,878)
Net cash provided by financing activities	**11,840**	**17,629**	**72,079**	**(678)**
Cash balance (Beginning of Period)	**12,528**	**7,073**	**10,738**	**49,124**
Difference	(5,455)	3,665	38,386	(4,120)
Cash balance (End of Period)	**7,073**	**10,738**	**49,124**	**45,004**
Marketable securites	**-**	**-**	**23,151**	**10,524**
Cash balance plus marketable securities (end of period)	**$7,073**	**$10,738**	**$72,274**	**$55,528**

Sources: Achaogen, Inc. and William Blair & Company, L.L.C. estimates

Appendix

ARK Diagnostics Contract

A key component to appropriate plazomicin dosing is the companion diagnostic developed in conjunction with ARK Diagnostics. The in vitro assay measures plazomicin blood levels necessary to optimize dosing. The companion diagnostic requires separate approval by the FDA's Center for Devices and Radiological Health and the European Commission.

The patents covering the diagnostic are co-owned by Achaogen and ARK Diagnostics. Achaogen is expected to pay between $1.0 million and $1.6 million in milestone payments for the achievement of certain development, manufacturing, and regulatory milestones. To date, Achaogen has paid out $0.7 million.

Upon approval, ARK Diagnostics has first rights to commercialize in the United States and EU, as well as manufacture and supply the assay worldwide. If ARK chooses not to pursue commercialization in the United States and EU, the option will be given to Achaogen, who is already entitled with all commercialization rights outside the United States and EU. However, if a commercialization plan between the two parties has not been established by January 2016, it is agreed that ARK will

supply Achaogen with a minimum supply of assay for at least two years following NDA approval, with the option to go to a third-party supplier for the subsequent three years. If by January 1, 2018, an agreement has not been reached, ARK will enter a technology transfer and license agreement allowing a third-party supplier to operate under a licensing agreement until the later of completion of services or January 1, 2020.

BARDA Contract

In August 2010, Achaogen received a grant from BARDA (the Biomedical Advanced Research and Development Authority within the U.S. Department of Health and Human Services, tasked with the development and purchase of vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies), to develop and manufacture plazomicin as a countermeasure for diseases caused by antibiotic-resistant pathogens (e.g., CRE, F. tularensis, and Y. pestis). Achaogen is entitled to receive $103.8 million, of which $39.5 million has been booked as of December 2013, leaving $64.3 million available. Further funding is expected, although the exact dollar amount has not been determined. The allocation will depend on plazomicin's safety profile and nonclinical biodefense studies. A decision on the grant allotment is expected by mid-2015.

Under the BARDA agreement, the U.S. government receives unlimited rights to use and disclose new data as well as nonexclusive, worldwide, royalty-free licenses for any compounds that are funded by the grant. Of note, the government does not have any rights to the composition of matter patents because those were developed before BARDA funding. Further, the government is not entitled to any sales royalties or other post-commercialization financial rights.

Other Government Contracts

In June 2007, Achaogen entered an agreement with the Defense Threat Reduction Agency (DTRA) to develop novel antibacterials for biodefense purposes. To date, Achaogen has received $33.5 million of the $35.4 million total. With $1.9M left in the contract, DTRA terminated the contract in 2012, and Achaogen continues to seek additional payments for related expenses. To date, no payments have been received.

In September 2008, Achaogen entered a five-year agreement with the U.S. National Institute of Allergy and Infectious Diseases, or NIAID, to develop novel antibacterials for biodefense purposes. To date, Achaogen has received $21.0 million. The contract expired in August 2013 and the company has terminated development of all related projects.

In May 2012, the company entered a one-year contract with the U.S. Army Medical Research Acquisition Authority, or USAMRAA. The grant, which expired in May 2013, yielded $2.5 million, which funded the Phase I study of ACHN-975.

Intellectual Property for Plazomicin; License from Isis Pharmaceuticals

Achaogen holds a portfolio of patents for plazomicin and its structural analogs, which includes composition of matter and methods of use for the treatment of infections. Specifically, the company holds U.S. Patent No. 8,383,596 (the '596 patent), the composition of matter patent for plazomicin. The patent was set to expire in November 2028, however with an extension granted by the USPTO, the patent is now expected to expire in June 2031. Dependent upon the timeline of its potential approval, the '596 patent may also qualify for an extension of up to 5 years under Hatch-Waxman. Outside the United States, patents have been granted in Australia, China, Eurasia, Japan, and South Korea, with applications pending in Brazil, Canada, China, Europe, Hong Kong, Israel, India, Mexico, and Taiwan; we believe these plazomicin composition of matter patents are expected to extend to at least 2028.

In 2006, Achaogen entered an exclusive license agreement with Isis Pharmaceuticals, Inc. to develop and commercialize aminoglycoside antibacterial compounds. In exchange for exclusive rights, Achaogen issued Isis $1.5 million in Series A convertible preferred stock. In addition, Achaogen will pay development and regulatory milestones totaling $19.5 million and up to $9.75 million for the first and second aminoglycoside products developed, respectively. Achaogen is expected to pay a low-double-digit share of non-royalty sublicensing revenues from any sublicense agreements. Royalties from sublicensing will cease once the threshold milestones have been met. To date, Achaogen has made milestone payments to Isis of $3.0 million, comprising $2.5 million in cash and $0.5 million in Series B preferred stock; in first quarter 2014, Isis also received a milestone payment of $4.0 million for the first dosed plazomicin patient from the Phase III CARE study. Achaogen is limited to payments of up to $20.0 million in total for a calendar year. If any product is approved for commercialization, Achaogen will pay Isis a low-single-digit royalty rate based on worldwide net sales of licensed or any sublicensed product.

Intellectual Property for LpxC Inhibitor; License From University of Washington
There are seven patents related to the anti-pseudomonal LpxC inhibitor. Achaogen holds six, with the last being in-licensed from the University of Washington (UW) and is co-owned by UW and Novartis Corp. The patents are as follows:

- U.S. patent application No. 12/635,551 pertains to chemical genus and methods of use of all LpxC inhibitor compounds. The patent has been filed and is expected to expire in June 2028.

- U.S. patent application No. 12/635,551 pertains to ACHN-975 and its analogues for methods of use and composition for the treatment of bacterial infection and is expected to expire in November 2031.

- International Patent Application No. PCT/US2013/040350 and PCT/US2013/040571 pertaining to the chemical genus of LpxC inhibitor compounds, but not ACHN-975, have been filed and are expected to expire in May 2033.

- Two U.S. patents (not disclosed) pertaining to the chemical genus of LpxC inhibitor compounds, but not ACHN-975, have been filed and are expected to expire in May 2034.

On December 1, 2006, the UW licensed patents covering the LpxC inhibitor antibacterial compounds to Achaogen. Of note, certain patents under this agreement are co-owned by UW and Novartis. Thus, exclusivity is subject to Novartis's rights to use the licensed patents and technology and to grant out-licenses. In January 2011, Achaogen amended the timing of milestone payments to UW, and, in return, UW received an up-front cash payment. Under the amended agreement, UW will receive milestone payments totaling $2.15 million for the first commercial product and $1.075 million for additional products. To date, Achaogen has paid out $150,000 in milestones for ACHN-975. Upon approval of ACHN-975 or other LpxC inhibitor antibacterial compounds, Achaogen will pay UW a royalty in the low single digits based on worldwide net sales. Last, Achaogen will pay UW mid single-digit to very-low-double-digit percentages for any sublicensing revenues. This agreement will remain binding until the last valid patent claim, which should carry until January 2024.

IMPORTANT DISCLOSURES

William Blair & Company, L.L.C. was a manager or co-manager of a public offering of equity securities within the prior 12 months.

William Blair & Company, L.L.C. is a market maker in the security of this company and may have a long or short position.

William Blair & Company, L.L.C. intends to seek investment banking compensation in the next three months from the subject company covered in this report.

Within the past 12 months William Blair & Company, L.L.C. has provided or is providing investment banking services to or has an investment services relationship with the subject company covered in this report.

Additional information is available upon request.

This report is available in electronic form to registered users via R*Docs™ at www.rdocs.com or www.williamblair.com.

Please contact us at +1 800 621 0687 or consult williamblair.com/Research-and-Insights/Equity-Research/Coverage.aspx for all disclosures.

Y. Katherine Xu attests that 1) all of the views expressed in this research report accurately reflect her personal views about any and all of the securities and companies covered by this report, and 2) no part of her compensation was, is, or will be related, directly or indirectly, to the specific recommendations or views expressed by her in this report. We seek to update our research as appropriate, but various regulations may prohibit us from doing so. Other than certain periodical industry reports, the majority of reports are published at irregular intervals as deemed appropriate by the analyst.

DJIA:	16,412.71
S&P 500:	1,865.09
NASDAQ:	4,127.73

The prices of the common stock of other public companies mentioned in this report follow:

AstraZeneca plc	$64.42
Cubist Pharmaceuticals, Inc.	$68.44
Forest Laboratories, Inc.	$90.56
Isis Pharmaceuticals, Inc.	$37.70
Johnson & Johnson	$98.42
The Medicines Company	$24.54
Merck & Co., Inc.	$56.12
Novartis AG	$82.51
Pfizer Inc.	$32.16
Tetraphase Pharmaceuticals, Inc.	$11.43

Current Ratings Distribution (as of 3/31/14)

Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	65%	Outperform (Buy)	13%
Market Perform (Hold)	32%	Market Perform (Hold)	2%
Underperform (Sell)	1%	Underperform (Sell)	0%

* Percentage of companies in each rating category that are investment banking clients, defined as companies for which William Blair has received compensation for investment banking services within the past 12 months.

The compensation of the research analyst is based on a variety of factors, including performance of his or her stock recommendations; contributions to all of the firm's departments, including asset management, corporate finance, institutional sales, and retail brokerage; firm profitability; and competitive factors.

OTHER IMPORTANT DISCLOSURES

Stock ratings, price targets, and valuation methodologies: William Blair & Company, L.L.C. uses a three-point system to rate stocks. Individual ratings and price targets (where used) reflect the expected performance of the stock relative to the broader market (generally the S&P 500, unless otherwise indicated) over the next 12 months. The assessment of expected performance is a function of near-, intermediate-, and long-term company fundamentals, industry outlook, confidence in earnings estimates, valuation (and our valuation methodology), and other factors. Outperform (O) – stock expected to outperform the broader market over the next 12 months; Market Perform (M) – stock expected to perform approximately in line with the broader market over the next 12 months; Underperform (U) – stock expected to underperform the broader market over the next 12 months; not rated (NR) – the stock is not currently rated. The valuation methodologies used to determine price targets (where used) include (but are not limited to) price-to-earnings multiple (P/E), relative P/E (compared with the relevant market), P/E-to-growth-rate (PEG) ratio, market capitalization/revenue multiple, enterprise value/EBITDA ratio, discounted cash flow, and others.

Company Profile: The William Blair research philosophy is focused on quality growth companies. Growth companies by their nature tend to be more volatile than the overall stock market. Company profile is a fundamental assessment, over a longer-term horizon, of the business risk of the company relative to the broader William Blair universe. Factors assessed include: 1) durability and strength of franchise (management strength and track record, market leadership, distinctive capabilities); 2) financial profile (earnings growth rate/consistency, cash flow generation, return on investment, balance sheet, accounting); 3) other factors such as sector or industry conditions, economic environment, confidence in long-term growth prospects, etc. Established Growth (E) – Fundamental risk is lower relative to the broader William Blair universe; Core Growth (C) – Fundamental risk is approximately in line with the broader William Blair universe; Aggressive Growth (A) – Fundamental risk is higher relative to the broader William Blair universe.

The ratings, price targets (where used), valuation methodologies, and company profile assessments reflect the opinion of the individual analyst and are subject to change at any time.

Our salespeople, traders, and other professionals may provide oral or written market commentary or trading strategies—to our clients and our trading desks—that are contrary to opinions expressed in this research. Certain outstanding reports may contain discussions or investment opinions relating to securities, financial instruments and/or issuers that are no longer current. Always refer to the most recent report on a company or issuer before making an investment decision. Our asset management and trading desks may make investment decisions that are inconsistent with recommendations or views expressed in this report. We will from time to time have long or short positions in, act as principal in, and buy or sell the securities referred to in this report. Our research is disseminated primarily electronically, and in some instances in printed form. Electronic research is simultaneously available to all clients. This research is for our clients only. No part of this material may be copied or duplicated in any form by any means or redistributed without the prior written consent of William Blair & Company, L.L.C.

THIS IS NOT IN ANY SENSE A SOLICITATION OR OFFER OF THE PURCHASE OR SALE OF SECURITIES. THE FACTUAL STATEMENTS HEREIN HAVE BEEN TAKEN FROM SOURCES WE BELIEVE TO BE RELIABLE, BUT SUCH STATEMENTS ARE MADE WITHOUT ANY REPRESENTATION AS TO ACCURACY OR COMPLETENESS OR OTHERWISE. OPINIONS EXPRESSED ARE OUR OWN UNLESS OTHERWISE STATED. PRICES SHOWN ARE APPROXIMATE.

THIS MATERIAL HAS BEEN APPROVED FOR DISTRIBUTION IN THE UNITED KINGDOM BY WILLIAM BLAIR INTERNATIONAL, LIMITED, REGULATED BY THE FINANCIAL CONDUCT AUTHORITY (FCA), AND IS DIRECTED ONLY AT, AND IS ONLY MADE AVAILABLE TO, PERSONS FALLING WITHIN COB 3.5 AND 3.6 OF THE FCA HANDBOOK (BEING "ELIGIBLE COUNTERPARTIES" AND "PROFESSIONAL CLIENTS"). THIS DOCUMENT IS NOT TO BE DISTRIBUTED OR PASSED ON TO ANY "RETAIL CLIENTS." NO PERSONS OTHER THAN PERSONS TO WHOM THIS DOCUMENT IS DIRECTED SHOULD RELY ON IT OR ITS CONTENTS OR USE IT AS THE BASIS TO MAKE AN INVESTMENT DECISION.

Equity Research Directory

John F. O'Toole, Partner Manager and Director of Research +1 312 364 8612
Kyle Harris, CFA, Partner Operations Manager +1 312 364 8230

CONSUMER

Sharon Zackfia, CFA, Partner +1 312 364 5386
Group Head–Consumer
Apparel and Accessories, Leisure, Restaurants

Jon Andersen, CFA, Partner +1 312 364 8697
Consumer Products

Daniel Hofkin +1 312 364 8965
Hardlines, Specialty Retail

Mark Miller, CFA, Partner +1 312 364 8498
E-commerce, Broad Assortment and Hardlines, Health and Beauty

Amy Noblin +1 415 248 2874
Apparel and Accessories

FINANCIAL SERVICES AND TECHNOLOGY

Adam Klauber, CFA +1 312 364 8232
Co-Group Head–Financial Services and Technology
Insurance Brokers, Property & Casualty Insurance

Robert Napoli, Partner +1 312 364 8496
Co-Group Head–Financial Services and Technology
Business Development Companies, Financial Technology, Specialty Finance

Christopher Shutler, CFA +1 312 364 8197
Asset Management, Financial Technology

GLOBAL INDUSTRIAL INFRASTRUCTURE

Nick Heymann +1 212 237 2740
Co-Group Head–Global Industrial Infrastructure
Multi-industry

Larry De Maria, CFA +1 212 237 2753
Co-Group Head–Global Industrial Infrastructure
Capital Goods

Nate Brochmann, CFA +1 312 364 5385
Commercial Services, Logistics/Transportation

Brian Drab, CFA, Partner +1 312 364 8280
Filtration and Water Management, Industrial Technology

Chase Jacobson +1 212 237 2748
Engineered Equipment, Engineering and Construction

Ryan Merkel, CFA +1 312 364 8603
Commercial Services, Industrial Distribution

GLOBAL SERVICES

Brandon Dobell, Partner +1 312 364 8773
Group Head–Global Services
Energy Services, Information Services, Marketing Services, Real Estate Services and Technology

Timo Connor, CFA +1 312 364 8441
Education Services and Technology

Timothy McHugh, CFA, Partner +1 312 364 8229
Consulting, HR Technology, Information Services, Staffing

HEALTHCARE

Ben Andrew, Partner +1 312 364 8828
Group Head–Healthcare
Medical Devices

Ryan Daniels, CFA, Partner +1 312 364 8418
Healthcare Information Technology, Healthcare Services

Margaret Kaczor +1 312 364 8608
Medical Devices

John Kreger, Partner +1 312 364 8597
Distribution, Outsourcing, Pharmacy Benefit Management

Tim Lugo +1 415 248 2870
Therapeutics

Amanda Murphy, CFA +1 312 364 8951
Diagnostic Services, Life Sciences, Pharmacy Benefit Management

Matthew O'Brien +1 312 364 8582
Medical Devices

John Sonnier, Partner +1 312 364 8224
Biotechnology

Brian Weinstein, CFA +1 312 364 8170
Diagnostic Products

Y. Katherine Xu, Ph.D. +1 212 237 2758
Biotechnology

TECHNOLOGY, MEDIA, AND COMMUNICATIONS

Jason Ader, CFA, Partner +1 617 235 7519
Co-Group Head–Technology, Media, and Communications
Hardware and Software Infrastructure

Bhavan Suri, Partner +1 312 364 5341
Co-Group Head–Technology, Media, and Communications
IT and Business Process Services, Software, Software as a Service

Rahul Bhangare +1 312 364 5066
IT and Business Process Services

Jim Breen, CFA +1 617 235 7513
Internet Infrastructure and Communication Services

Anil Doradla +1 312 364 8016
Semiconductors and Wireless

Justin Furby, CFA +1 312 364 8201
Software as a Service

Jonathan Ho +1 312 364 8276
Cybersecurity, Security Technology

Dmitry Netis +1 212 237 2714
Communications Equipment

Ralph Schackart III, CFA, Partner +1 312 364 8753
Digital Media, Internet

EDITORIAL

Steve Goldsmith, Head Editor +1 312 364 8540
Maria Erdmann +1 312 364 8925
Beth Pekol Porto +1 312 364 8924
Kelsey Swanekamp +1 312 364 8174
Lisa Zurcher +44 20 7868 4549

William Blair