COWEN
AND COMPANY

Biotechnology

# Achaogen

Equity Research

Initiating Coverage

April 8, 2014

**Price: $12.89** (04/7/2014)

**Price Target: $22.00**

**OUTPERFORM (1)**


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## Key Data

| | |
|---|---|
| Symbol | NASDAQ: AKAO |
| 52-Week Range: | $19.69 - 12.25 |
| Market Cap (MM): | $239.8 |
| Net Debt (MM): | $0.0 |
| Cash/Share: | $4.76 |
| Dil. Shares Out (MM): | 18.6 |
| Enterprise Value (MM): | $151.3 |
| ROIC: | NA |
| ROE (LTM): | NA |
| BV/Share: | NA |
| Dividend: | NA |

| FY (Dec) | 2013A | 2014E | 2015E |
|---|---|---|---|
| **Earnings Per Share** | | | |
| Q1 | - | $(0.80) | - |
| Q2 | - | $(0.29) | - |
| Q3 | - | $(0.32) | - |
| Q4 | $(0.58) | $(0.34) | - |
| Year | $(3.08) | $(1.40) | $(0.76) |
| P/E | NM | NM | NM |
| **Revenue (MM)** | | | |
| Q1 | - | $6.3 | - |
| Q2 | - | $6.5 | - |
| Q3 | - | $6.6 | - |
| Q4 | $6.2 | $6.6 | - |
| Year | $18.5 | $26.0 | $28.0 |
| EV/S | 8.2x | 5.8x | 5.4x |

# *Initiating Coverage: AKAO Looking To Make CRE A-OK*

## The Cowen Insight

We are initiating coverage of Achaogen with an Outperform rating and a 12-month price target of $22.00. Achaogen's unique pathogen-focused approach to antibiotic development differentiates it from competitors and has won strong support from regulatory agencies. We believe the ongoing pivotal Phase III clinical trial has a high likelihood of success and believe revenue potential to be strong.

## Achaogen is targeting deadly bacterial infections

Achaogen is developing lead product candidate plazomicin for the treatment of life-threatening infections caused by carbapenem-resistant Enterobacteriaceae (CRE). CRE are listed by the CDC as urgent threats to the healthcare system since carbapenems are used as the last resort antibiotics in combating ever increasing antibiotic resistance in bacteria. The global prevalence of CRE is rising rapidly but there are no efficacious treatments available for CRE infections. Mortality is high even with clinical intervention. Plazomicin is a next-generation aminoglycoside that has been engineered to overcome antibiotic resistance mechanisms. *In vitro* studies have demonstrated strong potency against CRE pathogens and the combination of PK/PD modeling and preclinical data from animal infection models suggest that plazomicin will be efficacious in human patients with CRE infections. The pivotal Phase III clinical trial was initiated in 1Q14 and is designed to demonstrate superiority of plazomicin as compared to colistin, currently the most frequently used antibiotic for CRE infections, in reducing 28-day all cause mortality. This is the first antibiotic trial to have a primary endpoint of superiority versus an active comparator. A well-established survival benefit will justify a premium pricing for plazomicin, in our opinion. Plazomicin is the only drug candidate being developed specifically for CRE pathogens so we believe Achaogen will face limited competition.

## Achaogen has received strong regulatory support

Achaogen has received an SPA for the ongoing pivotal study and plazomicin has received Fast Track Designation, which allows for a six-month priority review as well as a rolling submission. We believe the FDA recognizes the urgent need for a safe and efficacious treatment for CRE infections and therefore will likely be actively engaged in plazomicin's clinical development allowing for maximal flexibility. Both the FDA and the EMA have indicated that a single pivotal study will be sufficient to support regulatory filings. Top-line data from the pivotal study are expected in 1H17 and we expect plazomicin to enter the U.S. market in 2018.

## Achaogen has a strong balance sheet as well as financial support

In March 2014, Achaogen completed an IPO with total gross proceeds of approximately $82.8MM. Additionally, BARDA has committed a total of $103MM in grant funding to Achaogen, including $60MM to fund the ongoing pivotal study. The BARDA contract further contains an un-excercised option for additional funding so we believe Achaogen has secured sufficient capital to complete the Phase III program for plazomicin.

# At A Glance

## Our Investment Thesis

The pathogen-focused approach in developing plazomicin for the treatment of CRE infections, which cause high mortality due to lack of optimal treatments, has won Achaogen strong support from both the FDA and BARDA. The ongoing pivotal Phase III clinical trial is being conducted with an SPA and plazomicin has been granted Fast Track Designation. Additionally, BARDA has committed a total of $103MM in grant funding for plazomicin development, including $60MM to fund the pivotal study. Plazomicin has demonstrated strong potency against CRE pathogens and PK/PD modeling in combination with preclinical studies in animal infection models suggest a high likelihood of success in the pivotal study. The study is designed to demonstrate the superiority of plazomicin over currently available therapies. We believe a well-established survival benefit will entitle plazomicin to premium pricing and will provide Achaogen with strong revenue potential.

## Forthcoming Catalysts

- Initiation of the supportive efficacy trial by year-end 2014 and top-line data in 4Q15
- First and second interim analyses in the pivotal Phase III clinical trial in 2H15 and 2H16, respectively
- Initiation of the safety study after the first interim analysis

## Base Case Assumptions

- Patient enrollment proceeds as guided and top-line data from the pivotal Phase III clinical trial are reported in 1H17
- Plazomicin meets the primary endpoint of the pivotal study and receives regulatory approvals in both the U.S. and the EU
- Achaogen is able to price plazomicin at a premium upon launch

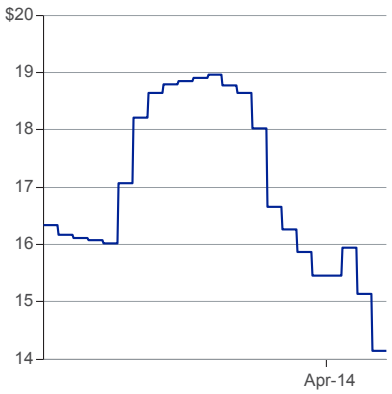
## Upside Scenario

- Achaogen achieves faster than expected patient enrollment and is able to expedite the clinical development process
- Plazomicin achieves faster than expected market penetration
- Achaogen is acquired at a premium for the company's clinical pipeline and technology

## Downside Scenario

- Patient enrollment in the pivotal Phase III study takes longer than expected, slowing down the overall clinical development process
- Plazomicin fails to meet the primary endpoint in the pivotal study in spite of strong *in vitro* and preclinical data
- Achaogen is unable to price plazomicin at a premium or receives strong push back from payers

## Price Performance




Source: Bloomberg

## Company Description

Achaogen is developing novel antibiotics for the treatment of multi-drug resistant (MDR) Gram-negative bacterial infections. The lead product candidate plazomicin, a next-generation aminoglycoside antibiotic, is in a pivotal Phase III clinical trial for bloodstream infections and nosocomial pneumonia caused by carbapenem-resistant Enterobacteriaceae (CRE). Achaogen has received an SPA from the FDA, as well as a grant of approximately $60MM from BARDA, for the pivotal study. The study was initiated in 1Q14 and top-line data are expected in 1H17. Achaogen has completed a Phase II clinical trial of plazomicin in cUTI and the drug candidate demonstrated non-inferiority to active comparator levofloxacin. *In vitro* and preclinical studies suggest that plazomicin will be efficacious in treating CRE infections and if the pivotal study succeeds, plazomicin will the be first antibiotic specifically developed for CRE pathogens. Achaogen also has preclinical programs for *Pseudomonas aeruginosa.*

## Analyst Top Picks

| | Ticker | Price (04/7/2014) | Price Target | Rating |
|---|---|---|---|---|
| Acadia Pharmaceuticals | ACAD | $20.69 | $33.00 | Outperform |
| Intra-Cellular Therapies | ITCI | $17.49 | $28.00 | Outperform |
| Horizon Pharma | HZNP | $13.51 | $20.00 | Outperform |

# Table Of Contents

# *Displays*

## Investment Thesis

### Plazomicin Targets An Indication With A High Mortality Rate And Limited Treatment Options

Achaogen's lead product candidate plazomicin is a next-generation aminoglycoside antibiotic being developed for the treatment of multi-drug resistant (MDR) Gram-negative bacterial infections. As the name indicates, these bacteria are resistant to the majority of currently available antibiotics and therefore the infections are difficult to treat. Achaogen's ongoing Phase III clinical trial is evaluating the safety and efficacy of plazomicin for the treatment of serious infections caused by carbapenem-resistant Enterobacteriaceae (CRE). Carbapenems are a class of β-lactam antibiotics and are typically used as the "last resort" for bacterial infections because of their broad spectrum and strong potency against both Gram-positive and Gram-negative strains. Therefore, the development of carbapenem resistance poses a significant threat to the public healthcare system since there would be virtually no efficacious therapeutics available for the treatment of infections caused by these pathogens.

Carbapenem resistant bacterial isolates are typically found in patients who have been admitted into acute healthcare settings, such as intensive care units (ICUs), and are suffering from nosocomial infections (infections acquired in the hospital setting). Due to the already compromised immune system of these patients, CRE can cause significant mortality – as high as 50% in patients with bloodstream infections. More concerning is the rapid spread of carbapenem resistance. The prevalence in the U.S. has increased significantly during the past decade. According to our physician consultants, some hospitals in heavily-affected geographic areas such as New York have identified approximately 50% of the hospital isolates to be carbapenem resistant.

Currently, a decade-old antibiotic, colistin (polymyxin E), and tigecycline (Tygacil, Pfizer, FDA approved in June 2005) are being used for the treatment of CRE infections based on their *in vitro* activity. However, both are far from optimal therapeutic options: colistin causes severe nephrotoxicity and tigecycline has been issued a boxed warning by the FDA due to increased mortality in treated patients. Moreover, analyses of accumulating clinical data continue to suggest that both drugs result in high mortality in patients with CRE infections.

**Significant Mortality With Currently Available Therapeutics**

*K. pneumoniae* Bloodstream Infections**

| Regimen | All-Cause Mortality |
|---|---|
| Colistin*** | 46% |
| Tigecycline*** | 47% |
| Aminoglycoside*** | 38% |
| Combination Therapy | 37% |

** Carbapenemase-producing *Klebsiella pneumoniae*

*** Agents are active *in vitro*

Source: Achaogen, Daikos et al., *Expert Rev. Anti. Infect. Ther.* 2012, 10:1393-1404

Plazomicin is engineered to overcome mechanisms which confer antibiotic resistance. The *in vitro* and preclinical studies that Achaogen has completed to date demonstrate the strong activity of plazomicin against CRE strains. The combination of PK/PD modeling and results from animal infection models further suggest that plazomicin has a high likelihood of being efficacious in human patients with CRE infections. As a result, we believe plazomicin has a high potential for success in the ongoing pivotal Phase III clinical trial and that it will provide a much needed solution for a significant global unmet medical need.

## Achaogen Has Received Strong Support From Regulatory Agencies

Achaogen has received a Special Protocol Assessment (SPA) for its ongoing pivotal Phase III clinical trial, which was initiated in 1Q14 and is evaluating the safety and efficacy (superiority) of plazomicin as compared to colistin for the treatment of bloodstream infections and nosocomial pneumonia caused by CRE. This single trial, if successful, will be sufficient to support an NDA filing in both the U.S. and EU. Additionally, plazomicin has received Fast-Track Designation from the FDA, which will entitle plazomicin to a six-month priority review as well as allow for rolling regulatory submissions. Achaogen has also received feedback on the clinical development program for plazomicin through the EMA's scientific advice procedure, indicating that the single pivotal Phase III clinical trial, if successful, will be acceptable to support a Marketing Authorization Application (MAA) in the EU.

Achaogen also plans to apply for the Qualified Infectious Disease Product (QIDP) designation for plazomicin. If granted, the designation will entitle plazomicin to an additional five years of market exclusivity (beyond existing exclusivity) in addition to the already granted Priority Review Status and Fast Track Designation.

We believe the strong support from the FDA and the EMA is due to the Agencies' clear recognition of the need for a novel antibiotic to address the global spread of CRE infections. We expect the FDA and the EMA to work actively and closely with Achaogen to expedite the clinical development and regulatory process for plazomicin.

## The Pivotal Phase III Clinical Trial Is Supported By A BARDA Grant

The development of plazomicin has strong financial support from the Biomedical Advanced Research and Development Authority (BARDA), a division of the Office of the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services. Achaogen's original contract was awarded in August 2010 with an initial funding commitment of $27.6 million for the first two years. In September 2012, BARDA exercised a contract option for an additional $15.8 million, increasing the total committed funding to $43.4 million through March 2014.

In April 2013, Achaogen further received an additional $60.4 million from BARDA for the pivotal Phase III clinical trial of plazomicin. The contract option was issued under BARDA's Broad Spectrum Antimicrobials (BSA) program. The new option announced in 2013 brings the total value of the contract to $103.8 million. Moreover, the BARDA contract contains an unexercised option for additional funding to support plazomicin's registry studies, including a safety study that Achaogen plans to initiate in 2015.

We expect the BARDA funding to cover a major portion of the expenses associated with the pivotal Phase III study, thereby significantly relieving Achaogen's financial spend on the clinical development of plazomicin.

Achaogen Has Strong Financial Support From BARDA

| Date | Awarded ($MM) | Cumulative Total ($MM) | Terms |
|---|---|---|---|
| August 2010 | 27.6 | **27.6** | Commited for the first two years with options for additional funding; effective through June 2014 |
| September 2012 | 15.8 | **43.4** | Effective through September 2014 |
| April 2013 | 60.4 | **103.8** | To support the plazomicin Phase III clinical trial |

Source: Achaogen & Cowen and Company

## Superiority Design Translates Into A Strong Competitive Advantage

In 1Q14, Achaogen initiated the Phase III clinical trial of plazomicin for the treatment of serious infections caused by CRE. The study is designed and powered to demonstrate the superiority of plazomicin over active comparator collistin in reducing 28-day all-cause mortality. This is the FIRST pivotal clinical trial in the antibiotic space to have a superiority design. We believe an established survival benefit will allow Achaogen to command a premium pricing for plazomicin

We believe an appropriate pricing comparator to plazomicin would be daptomycin (Cubicin, Cubist Pharmaceuticals), approved for the treatment of complicated skin and skin structure infections (cSSSI) and *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis. The drug is administered intravenously and the average length of treatment is approximately 14 days (7 to 24 days). The current wholesale acquisition cost (WAC) is $336.23 per 500mg in reconstituted solution. With doses of 4mg/kg for cSSSI and 6mg/kg for bloodstream infections, the calculated average cost per treatment cycle is approximately $4,700. In 2013, Cubist recorded U.S. daptomycin net revenue of $908 million. Daptomicin, as well as all other currently available antibiotics, received FDA approval based on non-inferiority as the primary efficacy endpoint.

We estimate a cost per treatment cycle of $15,000 in our revenue buildup model and believe the number is well justified if the pivotal Phase III study meets the primary endpoint of a statistically significant reduction in mortality. The patient outcome data from the study, if convincing, should present a strong case to both hospital formulary committees and payers. Pharmacoeconomic analyses also suggests that even with premium pricing, plazomicin should lead to a net cost savings for hospitals since any extra days that patients spend on mechanical ventilation and/or in ICUs are associated with significant expense.

Moreover, the small absolute prevalence of CRE infections in the U.S., estimated in our model to be approximately 80,000 per year, would in fact qualify as an Orphan disease. This point, we believe, would limit the impact that premium pricing would have on any one individual insurance payer. As a result, we would not expect to see pricing push back from payers.

Our revenue model suggests a market opportunity of approximately $500 million for plazomicin in the U.S. In Europe where companies typically face more pricing pressure and a less favorable reimbursement environment, we conservatively estimate that

plazomicin will be priced at a 70% discount to U.S. pricing and also achieve a lower market penetration.

The ex-U.S. CRE prevalence is higher than the U.S. prevalence and Achaogen expects the ongoing pivotal Phase III study to enroll the majority of its patients from ex-U.S. sites, predominantly Latin American and Eastern Europe. However, due to the lack of reliable information regarding patient numbers, physician treating behavior, and Achaogen's pricing power, we conservatively base our valuation mainly on the U.S. market and treat the ex-U.S. market as additional upside potential.

### Plazomicin Revenue Buildup Model

| | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E |
|---|---|---|---|---|---|---|---|---|
| **Plazomicin for Carbapenem-Resistant Enterobacterioceae (CRE)** | | | | | | | | |
| **U.S.** | | | | | | | | |
| Annual number of hospitalizations (MM) | 36.0 | 36.4 | 36.7 | 37.1 | 37.5 | 37.8 | 38.2 | 38.6 |
| *% of hospitalized patients who are infected with pneumonia* | *0.8%* | *0.8%* | *0.8%* | *0.8%* | *0.8%* | *0.8%* | *0.8%* | *0.8%* |
| Number of patients infected with nosocomial pneumonia (NP) (MM) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| *% of hospitalized patients who are infected with bloodstream infections* | *0.6%* | *0.6%* | *0.6%* | *0.6%* | *0.6%* | *0.6%* | *0.6%* | *0.6%* |
| Number of patients infected with bloodstream infections (BSI) (MM) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Total number of patients with NP and nosocomial BSI (MM) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| *% of carbapenem-resistant clones in nosocomial bacterial infections* | *4.0%* | *4.0%* | *4.1%* | *4.1%* | *4.2%* | *4.2%* | *4.2%* | *4.3%* |
| Annual number of carbapenem resistant NP and nosocomial BSI cases | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Annual number of CRE cases (MM) | 0.08 | 0.08 | 0.08 | 0.09 | 0.09 | 0.09 | 0.09 | 0.09 |
| *% of patients treated with plazomicin* | 2.0% | 8.0% | 14.0% | 18.0% | 20.0% | 22.0% | 24.0% | 25.0% |
| Number of patients treated with plazomicin (MM) | 0.002 | 0.007 | 0.012 | 0.015 | 0.017 | 0.020 | 0.022 | 0.023 |
| Cost per treatment cycle | $1,875 | $15,000 | $15,450 | $15,914 | $16,391 | $16,883 | $17,389 | $17,911 |
| **U.S. Total Plazomicin Revenue ($MM)** | **$3.0** | **$98.7** | **$181.5** | **$245.2** | **$286.3** | **$330.8** | **$379.2** | **$415.1** |
| **ROW** | | | | | | | | |
| Annual number of CRE cases (MM) | | 0.10 | 0.10 | 0.10 | 0.10 | 0.11 | 0.11 | 0.11 |
| *% of patients treated with plazomicin* | | 5.0% | 9.0% | 12.0% | 14.0% | 16.0% | 18.0% | 20.0% |
| Number of patients treated with plazomicin (MM) | | 0.005 | 0.009 | 0.012 | 0.015 | 0.017 | 0.020 | 0.022 |
| Cost per treatment cycle | | $10,500 | $10,815 | $11,139 | $11,474 | $11,818 | $12,172 | $12,538 |
| ROW Total Plazomicin Revenue ($MM) | | 51.8 | 98.0 | 137.3 | 168.3 | 202.1 | 238.9 | 278.9 |
| **ROW Royalty Revenue Booked by Achaogen ($MM) (15% - 25%)** | | **$7.8** | **$17.6** | **$24.7** | **$30.3** | **$40.4** | **$47.8** | **$55.8** |
| **WW Total Sales and Royalty Revenue Booked by Achaogen ($MM)** | **$3.0** | **$106.5** | **$199.1** | **$269.9** | **$316.6** | **$371.3** | **$427.0** | **$470.8** |

Source: Cowen and Company

## Patient Enrollment Will Take Time, But Could Accelerate

Achaogen has guided for patient enrollment completion for the Phase III clinical trial in 2016 and a top-line data announcement in 1H17. We project an NDA and MAA submission by year-end 2017 and FDA approval in mid-2018 based on a six-month Priority Review. We believe Achaogen will likely begin commercialization preparations before Phase III clinical trial completion and, therefore, should be able to promptly launch plazomicin in the U.S. by year-end 2018. In Europe, we conservatively estimate a longer regulatory review period and a commercial launch in 2019.

The two years required for patient enrollment is due to the small number of patients with clinically evaluable infections. Although the prevalence of CRE infections has increased dramatically in recent years, the absolute patient number is still low, and patients are concentrated in certain geographic areas. Additionally, Achaogen has established specific enrollment criteria to include only patients that are most likely to demonstrate clinical benefit from receiving plazomicin treatment (a detailed discussion can be found in the clinical trial design section of this report).

The outcome of antibiotic clinical trials is largely affected by the quality of enrolled patients. Therefore, we believe it is worth spending time ensuring that the pivotal study enrolls the optimal patient population. Although the current prevalence of carbapenem resistance may be low, we believe the rapid growth observed in the past decade will continue before an efficacious treatment becomes available. Therefore, we believe patient enrollment in the Phase III trial may potentially speed up.

There are two interim analyses built into the design of the Phase III clinical trial: the first interim is expected in 3Q15 upon completion of one third patient enrollment and the second interim is expected in 3Q16 after two thirds of targeted patients have been enrolled. Both an efficacy and futility evaluation will be conducted at both interim analyses.

## A Specialty Sales Force Should Be Able To Target The Hospital Setting

Plazomicin is being developed for hospital-based indications so a hospital-targeted specialty sales force will be required for commercialization. Moreover, CRE infections are concentrated within several "hot spots" in the U.S., which are typically metropolitan areas in states such as New York, Pennsylvania, New Jersey, Texas and California. This epidemiologic pattern should further help Achaogen in commercializing plazomicin independently with a small sales force to maximize market penetration. Our model assumptions have Achaogen hiring approximately 30 sales representatives by year-end 2018 for the U.S. launch of plazomicin. In Europe, we estimate that Achaogen will enter into a partnership and receive back-end tiered royalties on plazomicin sales.

## Upcoming Milestones Will Provide Sufficient News Flow In The Near Term

The Phase III clinical trial for CRE is expected to take three years to complete with top-line data estimated in 1H17. Achaogen will however have the following upcoming milestones, which we believe will provide catalysts for the stock.

Achaogen Upcoming Milestones

| Event | Expected |
|---|---|
| **Plazomicin** | |
| Supportive efficacy trial initiation | YE14 |
| First interim analysis of Phase III clinical trial | 2H15 |
| Supportive efficacy trial top-line data | 4Q15 |
| Second interim analysis of Phase III clinical trial | 2H16 |
| Phase III clinical trial top-line data | 1H17 |
| **Antipseudomonal programs** | |
| At least one IND | 2015 |

Source: Achaogen & Cowen and Company

## Carbapenem-Resistant Enterobacteriaceae (CRE)

Enterobacteriaceae is a group of bacteria that include both harmless strains that exist as part of the natural gut flora in human intestines as well as disease-causing strains. Three species of Enterobacteriaceae, *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*, make up approximately 80% to 95% of all isolates identified in the clinical setting. Carbapenem-resistant Enterobacteriaceae (CRE) refers to the bacteria that have developed resistance to the carbapenem class of antibiotics, which are normally considered the antibiotic class of last resort for the treatment of bacterial infections. Very limited options remain once carbapenem resistance has developed so CRE poses a significant threat worldwide.

Due to the high level of resistance found in almost all classes of currently available antibiotics, CRE has a much higher mortality rate than other bacterial infections caused by carbapenem-susceptible strains. A clinical study compared patients with bloodstream infections caused by CRE, extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae, or susceptible *Klebsiella pneumoniae* (Ben-David *et al*., *Clin. Microbiol. Infect* 2012). The study found the infection-related mortality rate to be 48% for CRE, 22% for ESBL producers and 17% for susceptible *Klebsiella pneumoniae*, respectively.

**CDC Antibiotic-Resistant Bacteria Threat Level Scale**

| |
|---|
| **URGENT: Immediate public health threats that require urgent and aggressive action** |
| *Clostridium difficile* |
| **Carbapenem-resistant Enterobacteriaceae (CRE)** |
| Drug-resistant *Neisseria gonorrhoeae* |
| **SERIOUS: Require prompt and sustained action to ensure the problem does not escalate** |
| Multi-drug resistant Acinetobacter |
| Drug-resistant Campylobacter |
| Extended spectrum beta-lactamase producing Enterobacteriaceae (ESBLs) |
| Vancomycin-resistant Enterococcus (VRE) |
| Multi-drug resistant *Pseudomonas aeruginosa* |
| Drug-resistant non-typhoidal Salmonella |
| Drug-resistant Salmonella Serotype Typhi |
| Drug-resistant Shigella |
| Methicillin-resistant *Staphylococcus aureus* (MRSA) |
| Drug-resistant *Streptococcus pneumoniae* |
| Drug-resistant tuberculosis |
| **CONCERNING: Careful monitoring and prevention is required** |
| Vancomycin-resistant *Staphylococcus aureus* (VRSA) |
| Erythromycin-resistant Group A Streptococcus |
| Clindamycin-resistant Group B Streptococcus |

Source: Centers for Disease Control and Prevention (CDC)

As a result of the severity of the infections and the lack of effective treatment options, CRE is listed as one of the three "Urgent" threats by the Centers for Disease Control (CDC). In contrast, Methicillin-resistant *Staphylococcus aureus* (MRSA), which is one of the most frequently targeted bacterial species by biotechnology and pharmaceutical companies in drug development, is categorized one step lower as a "Serious" threat. This ranking speaks to the urgency required in developing new

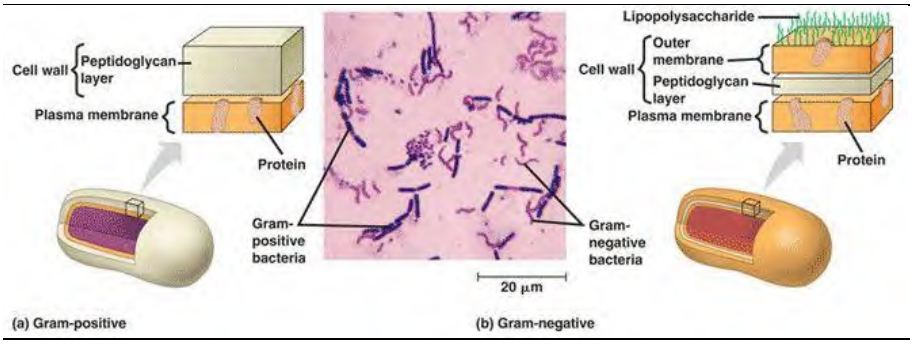
antibiotics to combat CRE. In addition to Achaogen, several other companies are now investing in the development of antibiotics against MDR Gram-negative pathogens (a detailed discussion can be found in the "Competitive Landscape" section of this report). We estimate the global market opportunity for new antibiotics with potency against a broad spectrum of MDR Gram-negative pathogens should be larger than that for MRSA Gram-positive pathogens, given the increased severity and associated mortality of MDR Gram-negative infections. The Gram-negative commercial landscape is less crowded than the Gram-positive market due to the greater challenge companies' face technologically when developing antibiotics targeting Gram-negative pathogens.

### Gram Positive vs. Gram Negative

Bacteria that are responsible for infections are typically classified by Gram staining, which is a laboratory procedure that employs a violet dye for the differentiation of bacterial species into two major categories. Bacteria that retain the violet color from the dye are referred to as Gram-positive and those not taking up the violet dye are labeled as Gram-negative. This difference stems from the chemical and physical differences between species of bacteria. The outer cell walls of Gram-positive bacteria are thick and composed of complex cross-linked proteins and carbohydrates. Teichoic acid is an important polysaccharide present in the Gram-positive cell wall which displays the color violet when stained. In contrast, Gram-negative cells have three outer layers that compose the cell envelope. The outer-most layer resembles a cytoplasmic membrane with a typical tri-laminar structure. The middle layer is the cell wall composed of a thin lipopolysaccharide layer. The inner most layer is composed of proteins, lipoproteins, and phospholipids.

Gram-negative bacteria, with porin channels localized on their membrane that gate-out large molecules, are less sensitive than Gram-positive bacteria to large antibiotics such as vancomycin and bacitracin.

**Gram Staining And Cell Wall Composition**




Source: Quia

### Infections Caused By Gram-Negative Bacteria

The following indications, listed from less severe to more severe, are caused by Gram-negative bacteria and are the most common targets in antibiotic clinical development.

#### Complicated Urinary Tract Infection (cUTI)

Urinary tract infections (UTIs) are the most common type of bacterial infection and occur when bacteria multiply and spread in the urinary tract system (kidneys, ureters,

bladder and urethra). Depending on the factors that trigger a UTI, they may be classified as uncomplicated or complicated. Complicated UTIs (cUTIs) are severe, recurrent and difficult to treat infections that occur in both men and women. cUTIs are most often caused by *Escherichia coli*, with Klebsiella, *Proteus mirabilis*, Citrobacter, *P. aeruginosa*, Enterobacter and enterococcus species contributing to the total number of infections . Uncomplicated UTIs such as bladder (cystitis) or kidney (pyelonephritis) infections are most often caused by *Escherichia coli* and affect mainly women. Multiple symptoms of UTIs may appear suddenly and simultaneously. Examples of symptoms include a frequent urge to urinate, painful or burning sensation during urination, urine with strong odor, urine that is cloudy or bloody in appearance, pain in the pelvic or lower back area, discomfort or pressure in the lower abdomen, and development of fever.

The main causes for cUTIs are frequent catheter usage, anatomical abnormalities, and bladder and kidney dysfunction including kidney transplants. The duration of catheter usage whether in the hospital or in the out-patient setting is directly correlated with the risk of contracting a cUTI. Medical conditions that increase the risk of cUTIs include kidney disorders, kidney stones, sickle-cell anemia, urinary tract abnormalities, and dysregulation of the immune and neurological systems.

### Intra-Abdominal Infections (IAI)

Intra-abdominal infections (IAIs) are also classified as uncomplicated and complicated. Uncomplicated IAIs are cases where the infectious process is limited to the gastrointestinal tract and does not proceed to the peritoneal cavity. Complicated IAIs (cIAIs) are infections that extend beyond the source organ into the peritoneal space and result in peritoneal inflammation associated with localized or diffuse peritonitis. Common cIAI pathogens are bacteria that are part of the normal gut flora but are no longer contained, including *Escherichia coli*, *Klebsiella*, *Enterococci*, *Bacteroides fragilis* and Clostridium among others.

Similar to cUTIs, cIAIs are also a challenge to treat in intensive care medicine and are responsible for 20% of severe sepsis cases. Clinical symptoms of IAIs typically present as abdominal pain, anorexia, fever, abdominal distention and tenderness, hypoactive or faint bowl sounds and leukocytosis. Ultrasound or CT scans may also be employed for evaluation.

### Nosocomial pneumonia (NP)

Nosocomial pneumonia (NP), also known as hospital-acquired bacterial pneumonia (HAP) and defined as pneumonia contracted by a patient after being admitted to a hospital for 48 to 72 hours, is the second most commonly occurring infection and accounts for up to 20% of all nosocomial infections. Ventilator-associated pneumonia (VAP) is a subtype of HAP in patients who contract pneumonia after receiving mechanical ventilation for at least 48 hours. VAP occurs in 28% of patients who receive mechanical ventilation and the probability of developing VAP decreases after the initial five days of mechanical ventilation. Fifteen percent to 50% of mortalities involving VAP are attributed directly to VAP rather than primary causes.

Gram-negative bacterial infections are responsible for 64% of all HAP and VAP episodes. *Pseudomonas aeruginosa* infections account up for 21% of the cases and *S. aureus* is responsible for 20% of the Gram-negative VAP cases. In the intensive care unit (ICU), *Klebsiella pneumoniae* accounts for 18.1% of all infection cases.

### Bloodstream infections (BSI)

BSI is a serious infection caused by bacteria that enter the bloodstream, which is sterile under normal conditions. BSI usually occurs as a severe complication of infections such as pneumonia or meningitis, or when bacteria enter the blood during surgical procedures, or through catheters that are placed in patients' arteries or veins. Bacteria in the blood can cause sepsis, which is a systemic inflammatory response that is associated with a high mortality rate. According to data from Johns Hopkins Hospital, an estimated 80,000 patients with central-line catheters develop BSIs in the U.S. each year and result in 31,000 deaths. The annual cost of treating BSIs is approximately $3 billion.

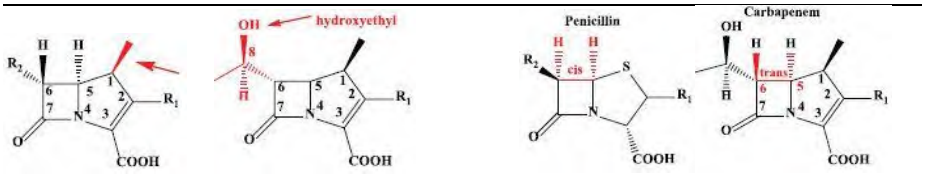
## Carbapenems, The Last Line Of Defense In Fighting Bacterial Infections

Carbapenems are a class of β-lactam antibiotics and have the broadest antibacterial spectrum activity and the greatest potency against both Gram-positive and Gram-negative bacteria in the β-lactam class. Other members of the β-lactam family include cephalosporins, monobactams, and penicillins. Thienamycin, the first carbapenem discovered in a search for β-lactamase inhibitors, was isolated as a natural product derived from a Gram-positive bacterium *Streptomyces cattleya*. Characterization of thienamycin demonstrated that the antibiotic possesses β-lactamase inhibiting activity and therefore is resistant to hydrolysis by most β-lactamases. Thienamycin has served as the parent compound for subsequent carbapenems that have been developed, including imipenem (imipenem/cilastatin as Primaxin, Merck, FDA approved in 1985), meropenem (Merrem, Dainippon Sumitomo, FDA approved in July 1996), ertapenem (Invanz, Merck, FDA approved in November 2001), and doripenem (Doribax, JNJ, FDA approved in October 2007).

Earlier generations of carbapenems were only available as an intravenous formulation. However the discovery, development and synthetic modification of additional carbapenems eventually led to the discovery of orally available carbapenems with enhanced stability. Chemical characterization studies have revealed that the potency and spectrum of activity of carbapenems are mostly determined by the carbon atom at the C-1 position whereas stability against β-lactamases is typically dependent on the hydroxyethyl $R_2$ side chain. Moreover, the *trans*-configuration of the β-lactam at C-5 and C-6 enhances the stability of carbapenems in comparison to the penicillins and cephalosporins. Newly developed carbapenems take advantage of these characteristic studies and are more potent against both Gram-positive bacteria and Gram-negative bacteria.

Carbapenems are often considered "last-line agents" against multi-drug resistant pathogens or used only in patients with complicated infections. Due to the mechanism of action, carbapenems are often used in combination with other antibiotics to treat serious, life-threatening, infections.

**Carbapenem Chemistry**




C1 increases potency | R2 increase stability | Improvements from penicillin

Source: Antimicrobial Agents and Chemotherapy

Carbapenems enter the periplasmic space of Gram-negative bacteria through the outer membrane proteins (OMPs, also known as porins) to inhibit penicillin binding proteins (PBPs), which are enzymes that catalyze the formation of peptidoglycan in the bacterial cell wall. This inhibition leads to disruption of the balance between the formation and autolysis of the cell wall and eventually to bacterial cell death due to osmotic pressure. Compared to other members of the β-lactam family, carbapenems are relatively resistant to hydrolysis by most β-lactamases.

Currently available carbapenems can be divided into three groups based on their varying affinities to PBPs and the resulting differences in their activity on pathogens.

- **Group 1**: Carbapenems with limited activity against Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter* but suitable for the treatment of community acquired infections caused by ESBL-producing bacteria (e.g. ertapenem)

- **Group 2**: Carbapenems with higher activity against Gram-negative bacteria and therefore particularly suitable for the treatment of nosocomial infections (e.g. imipenem, meropenem, biapenem and doripenem)

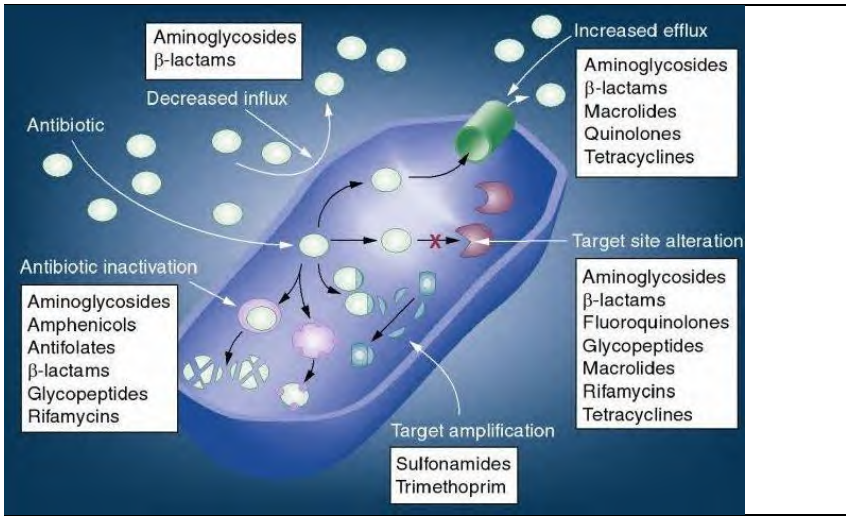
- **Group 3**: Investigational carbapenems with activity against MRSA

β-lactam antibiotics form the core of hospital-based antimicrobial therapy but their use is increasingly compromised by acquired β-lactam resistance, especially in Gram-negative bacteria such as Enterobacteriaceae and *Pseudomonas aeruginosa*. In a recent survey conducted by The Center for Disease Dynamics, Economics & Policy (CDDEP), which involved thousands of patients from hospitals around the world, Gram-negative bacteria were found in 60% of clinical isolates in intensive care units. The risk of VAP increases with the increasing duration of mechanical ventilation and often the infectious organism responsible after the first five days is almost universally due to resistant organisms such as MRSA, multi-drug resistant (MDR) *P. aeruginosa* and MDR Acinetobacter.

### Carbapenemases Are The Main Reason For Carbapenem Resistance

Bacteria develop antibiotic resistance with random mutations as they divide and proliferate. Additionally, bacteria may also acquire DNA plasmids or small fragments of DNA from other bacteria or viruses that encode for resistance genes. Gram-negative bacteria can gain carbapenem resistance through several mechanisms, including increased expression of efflux pumps on the cell membrane that actively expel carbapenems out of bacteria, loss of porin protein on the bacterial outer cell membrane that prevents carbapenems from entering bacteria, mutations in PBP protein and/or decreases in PBP transcription, and most frequently, expression of carbapenemases.

**Bacterial Mechanisms Of Resistance**

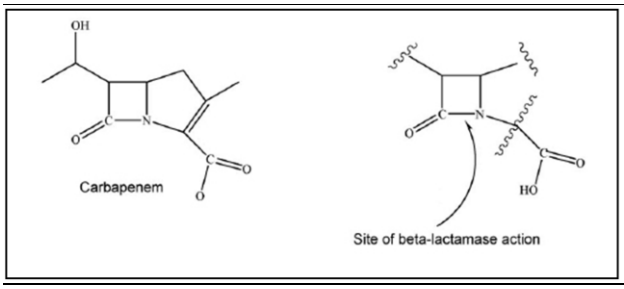



Source: Medscape

The major mechanism of carbapenem resistance is through the bacteria's expression of enzymes, namely carbapenemases (specific β-lactamases), that target and hydrolyze the β-lactam ring structure of carbapenems (the square ring in the below carbapenem chemical structure). The breaking of the β-lactam ring inactivates carbapenems and as a result, renders the antibiotics ineffective in treating bacterial infections. Listed below are a few major carbapenemases that have been identified with varying geographic distribution:

- ***Klebsiella pneumonia* carbapenemase (KPC)**: reported in the U.S. and worldwide; high prevalence in the U.S. and Greece
- **Metallo-enzymes (Verona Integrin-encoded Metallo-β-lactamase, VIM):** reported worldwide; high prevalence in south Europe and Asia
- **Oxacillinase (OXA) type carbapenemases:** identified mostly in Mediterranean and European countries and India
- **New Delhi Metallo-β-lactamase-1 (NDM-1):** a member of the Metallo-β-lactamase class, recently identified in the UK, India and Pakistan, but prevalent worldwide

**Carbapenem Inactivation By β-Lactamase**




Source: University of Illinois at Chicago

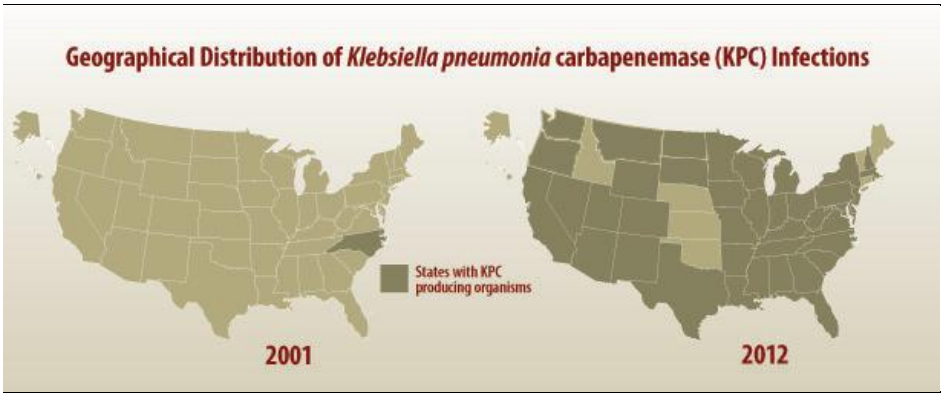
Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the most common type of CRE in North America and the majority of CREs in this region are due to *Klebsiella*

*pneumoniae* carbapenemases (PKCs). In terms of strains in the Enterobacteriaceae family, *Klebsiella pneumoniae* and *Escherichia coli* are the two major bacteria that produce carbapenemases. CRE are resistant to most currently available antibiotics and the resistance is spreading rapidly, thereby posing a significant threat to the healthcare system.

### Prevalence Of Carbapenem Resistance Is Increasing Rapidly

As mentioned previously, CRE infections predominantly occur in the hospital setting in patients who are receiving treatments for other conditions. These patients tend to be on ventilators, or have urinary catheters or intravenous catheters. Additionally, they may be taking long courses of β-lactam antibiotics, thereby significantly elevating the risk of contracting a CRE infection. Since its first identification in the U.S., the prevalence of CRE has been increasing rapidly, particularly during the past decade.

**Spread Of KPC Infections In The U.S.**



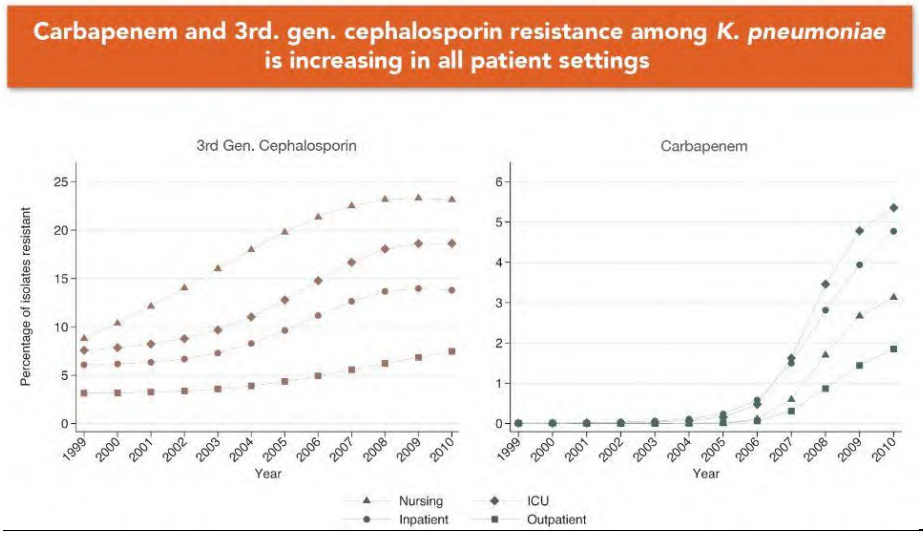

Source: Center for Disease Control and Prevention (CDC)

Data from the National Nosocomial Infection Surveillance (NNIS) system suggest that the U.S. prevalence of CRE was low before 1990, with 2.3% of 1,825 Enterobacter isolates resistant to imipenem. However, among isolates reported to the National Healthcare Safety Network (NHSN) in 2006–2007, up to 4.0% of *Escherichia coli* and 10.8% of *Klebsiella pneumoniae* isolates that were associated with certain device-related infections had gained carbapenem resistance. In the Meropenem Yearly Susceptibility Test Information Collection Program, meropenem resistance increased from 0.6% in 2004 to 5.6% in 2008.

Based on data published by the Centers for Disease Control and Prevention (CDC), approximately 18% of long-term acute care hospitals and approximately 4% of short-stay hospitals in the U.S. detected at least one case of CRE infection during the first half of 2012. A weekly report from the CDC calculated the proportion of CRE in all Enterobacteriaceae infections in two surveillance systems: 1) the NNIS and the NHSN (for 2001 and 2011, respectively) and 2) the Surveillance Network–USA (TSN) (for 2001 and 2010). The results indicated that CRE rates increased from 1.2% in 2001 to 4.2% in 2011 in NNIS/NHSN and from 0% in 2001 to 1.4% in 2010 in TSN. Most of the increases were observed in Klebsiella species (from 1.6% to 10.4% in NNIS/NHSN).

The healthcare industry is especially concerned with the recent increase in the number of cases of *Klebsiella pneumoniae* that are resistant to carbapenems and 3rd generation cephalosporins.

Increasing U.S. Cases Of Carbapenem- And 3rd Generation Cephalosporin-Resistant *K. Pneumoniae*




Source: The Center for Disease Dynamics, Economics & Policy (CDDEP)

Moreover, many CRE cases may have evaded recognition, since detection of carbapenem resistance requires proper laboratory analysis, which may be lacking at small hospitals or nursing homes. Additionally, it is not yet mandatory to report CRE cases to the CDC. Only a few states are tracking CRE cases even though the CDC has urged states to do so. As a result, CRE prevalence as well as the presence of KPC-producing isolates may have been underestimated by earlier reports.

### Reasons For Increased Carbapenem Resistance

Bacterial resistance to antibiotics is a natural phenomenon and many pathogens will eventually develop mechanisms to overcome even the most potent antibiotics in the clinical arsenal. The development of resistance and the spread of resistant bacterial strains are most often caused by the misuse or overuse of antibiotics both in the hospital setting and in the community or outpatient setting. CRE incidence and prevalence are both higher in countries where antibiotic use and distribution are not strictly regulated.

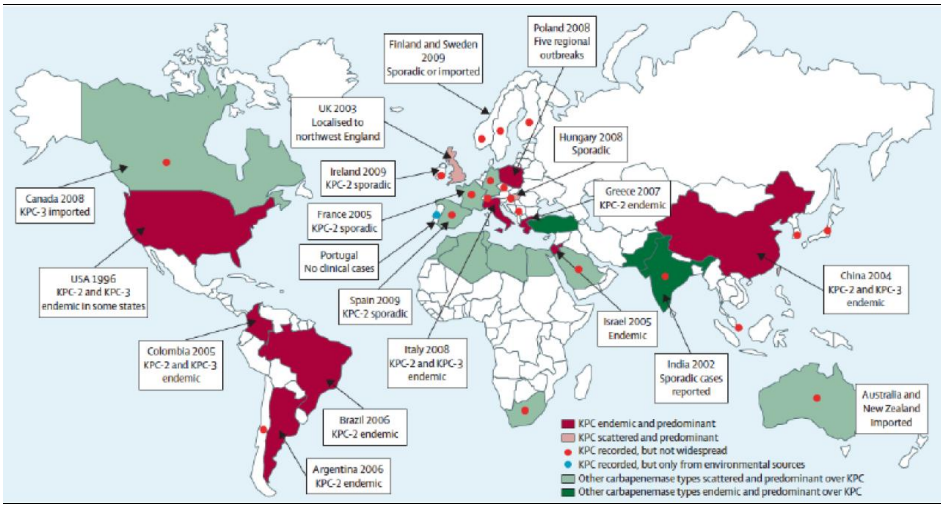
The genes that encode for β-lactamases often reside in mobile genetic elements such as plasmids that can readily be transferred between bacteria. As a result, they have the potential to spread widely to related bacterial species through horizontal gene transfer, which is a different manner of gene transfer from traditional reproduction (referred to as vertical gene transfer from a parental generation to offspring). Horizontal gene transfer is common among bacteria and is considered the primary reason for antibiotic resistance.

### Carbapenem Resistance Is A Global Threat

CRE has been reported worldwide and there have been multiple nosocomial infection outbreaks with cabapenemase-producing Enterobacteriaceae. As we have discussed in an earlier part of this report when we introduced different classes of carbapenemases, the most frequently identified type of carbapenemase varies by country. However, since most of the enzymes are located in mobile genetic elements and can be easily acquired by most bacterial strains, carbapenem resistance has spread globally. The following map highlights regions and countries where a high CRE

prevalence has been detected. In Europe, CRE prevalence varies significantly across different countries, from a high prevalence in Greece and Italy to a low prevalence in Nordic countries.

**Global CRE Prevalence Map**




Source: Achaogen; *The Lancet Infectious Diseases*, 2013. 13(9): 785 - 796

## Starting In Hospitals But Spreading To The Community

Hospitals remain the primary transmission sites for CRE infections and exposure to hospital environments and antimicrobials are the two most prominent risks for CRE infection. The most common cases of CRE are healthcare-associated infections (HAIs) caused by *Klebsiella pneumoniae* and *Escherichia coli*. Patients admitted to long-term acute care facilities that require long-term parenteral administration and/or ventilator use to aid in breathing have a further elevated risk for CRE infections when compared to other hospitalized patients.

The spread of CRE from hospitals to the community in recent years is particularly concerning since monitoring and control of bacterial infections and transmission in the community is significantly more difficult than in the hospital setting. Although there are no reliable data available, the current CRE prevalence in the community setting should still be low. However, as the chart on the previous page indicates, the number is also growing at a fast pace. Moreover, Enteobacteriaceae are the most frequent causes of community infections and human-to-human transmission is common. Therefore, it is reasonable to hypothesize that the spread of CRE in the community setting could be rapid. There are concerns that CRE may replicate the spreading pattern observed with MRSA: resistance initially occurring among the most severely ill and hospitalized patients, then spreading to other patients and ultimately reaching the community.

## Available Treatments

There are no FDA-approved antibiotics specifically for the treatment of CRE. Studies have suggested that colistin, tigecycline, and fosfomycin are the most potent agents against CRE strains amongst the currently available antibiotics. A study conducted in 2011 (Livermore *et al*, Int. J. Antimicrob Agents) evaluated the activity of the aforementioned antibiotics in combination with several other antibiotics against 81

CRE isolates from the U.K. The study found that colistin, tigecycline, and fosfomycin inhibited 92.6%, 46.9%, and 60.5% of the isolates, respectively. The study concluded that the activity of colistin, tigecycline and fosfomycin was unrelated to the isolates' carbapenem resistance mechanisms.

From a separate study, among 344 isolates of KPC-producing Enterobacteriaceae sent to the CDC for evaluation from January 2007 to October 2009, 312 (91%) and 304 (88%) had an MIC of ≤ 2mg/mL for colistin and tygecycline, respectively. Additionally, some aminoglycosides have been used for the treatment of CRE as well. However, none of these treatment options has been evaluated in well-controlled, prospective clinical trials.

### Colistin

Colistin (polymyxin E) is a bactericidal antibiotic that disrupts the outer membrane of Gram-negative bacteria by binding to lipopolysaccharides and phospholipids in the membrane. It was isolated in the 1940's and became clinically available for the treatment of Gram-negative infections such as those caused by *Pseudomonas aeruginosa* in late 1950's. However, colistin causes severe side effects such as nephrotoxicity and neurotoxicity. As a result, its usage decreased after aminoglycosides became available. However, colistin has regained favor from physicians in recent years because of the increased resistance in bacteria to other available antibiotics.

Colistin is currently used as a last resort option against MDR strains. However, resistance to colistin, although still rare, is increasing with reported colistin resistance in isolates of KPC- or VIM-producing *Klebsiella pneumoniae* from different countries around the world. Additionally, several enterobacterial species, such as *Proteus spp*., are known to have natural colistin resistance.

Furthermore, the pharmacokinetic (PK) profile of colistin in humans has not been well characterized and it adds an additional layer of complexity in the use of colistin for the treatment of CRE infections. Colistin is administered as colistimethate sodium, a prodrug that is subsequently hydrolyzed to colistin. The serum half-life of the prodrug is approximately two hours whereas the active drug has a much longer half-life and undergoes reabsorption in the renal tubular cells. Due to this complicated PK profile, it is difficult to conduct dosing optimization, particularly in critically ill patients with renal failure or other alterations in either drug distribution or metabolism.

### Tigecycline

Tigecycline (Tygacil, Pfizer – FDA approved in June 2005) is the first from the class of glycylcyclines to receive FDA approval. It has a similar structure as the tetracyclines and functions as a bacteriostatic antibiotic by binding to the ribosomal subunit of bacteria to inhibit their protein synthesis. With a broad spectrum covering both Gram-positive and Gram-negative infections, tigecycline was developed in response to the increasing rates of antibiotic resistance. It received initial FDA approval for the treatment of complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (cIAI), and in February 2009 for the treatment of community-acquired bacterial pneumonia (CABP). However, it does not have activity against *Pseudomonas spp.* or *Proteus spp.*

The efficacy of tigeclycline in treating bloodstream Enterobacteriaceae infections may be limited by the drug's PK profile. The peak serum concentration of tigecycline with standard IV dosing is between 0.6μg/mL and 0.9μg/mL, lower than the susceptibility breakpoint of 1μg/mL proposed by the European Committee on Antimicrobial

Susceptibility Testing (EUCAST). Although higher doses can help achieve higher serum concentrations, it is difficult to reach the optimal effectiveness by maintaining the serum level for an adequate period of time since the drug is distributed quickly to other tissues.

Moreover, based on a pooled analysis from tigecycline comparative trials for both FDA-approved and non-approved indications that demonstrated increased overall mortality with tigecycline treatment, the FDA approved a new Boxed Warning to be added to the drug's label in September 2013. The FDA advises that tigecycline be reserved for use in situations when alternative treatments are not suitable.

### Fosfomycin

Fosfomycin is a bactericidal antibiotic that inhibits the production of bacterial wall precursors. It has a broad spectrum of activity against both Gram-positive and Gram-negative bacterial strains but one notable exception is *Acinetobacter baumannii*. Fosfomycin is available as an oral powder in the U.S. and is only indicated for uncomplicated urinary tract infections, with a pharmacokinetic profile that is particularly favorable in urine. However, in light of the recent emergence of MDR pathogens, fosfomycin has been studied for additional indications, including uncomplicated and complicated UTIs caused by ESBL-producing Enterobacteriaceae or carbapenem-resistant *Klebsiella pneumoniae*.

Data from recent studies conducted in Greece and the U.S., which utilized the EUCAST MIC breakpoint of susceptibility (≤32 mg/L), demonstrated that approximately 54% to 93% of the carbapenemase- or MBL-producing *Klebsiella pneumoniae* isolates tested were susceptible to fosfomycin, although many had borderline susceptibility. However, the rate of resistance in *Klebsiella pneumonia* may also be high for fosfomycin. In fact, the rate of chromosome-located gene mutations that contribute to fosfomycin resistance is higher than that of other antibiotic agents as determined by *in vitro* studies.

### Aminoglycosides

Some aminoglycosides have been used for the treatment of CRE based on *in vitro* activity but their susceptibilities are unpredictable due to the lack of clinical data. Most CRE strains, except those with OXA-48 β-lactamase, also possess multiple aminoglycoside-modifying enzymes that inactivate aminoglycosides. In particular, CRE strains with NDM-1 carbapenemase typically also have 16S rRNA methylases and therefore have complete aminoglycoside resistance.

In summary, the currently available treatment options for CRE are highly limited and far from optimal. As a result, in addition to strengthening the preventive measure to slow down the spread of CRE, there is an urgent need for a novel antibiotic that is potent and safe for this indication. Achaogen's lead candidate plazomicin will potentially become the first antibiotic to receive FDA approval specifically for the indication of CRE if Phase III clinical development is successful.

Limitations Of Currently Available Therapies For CRE

| Treatment | All-Cause Mortality* | Key Limitations |
|---|---|---|
| Colistin | 46% | Nephrotoxic, target attainment difficult, growing resistance |
| Tigecycline | 47% | Bacteriostatic, increased risk of death in meta-analysis |
| Fosfomycin | N/A | Limited clinical data, easy to develop resistance |
| Aminoglycoside | 38% | Often not active due to co-expression of aminoglycoside resistance mechanisms |

* *Klebsiella pneumoniae* bloodstream infections

Source: Achaogen; Daikos et al., Expert Rev. Anti. Infect. Ther. 2012, 10:1393-1404 & Cowen and Company

### Combination Therapies Are Recommended

Combination therapies are highly recommended for the treatment of CRE infections to prevent the development of resistance in addition to maximizing the rate and extent of cidal activity. Polymyxins (colistin or polymyxin B) are usually included in combination therapies due to the high *in vitro* susceptibility that most CRE demonstrate against this class of antibiotics. Although there is no well-established clinical evidence to support the benefit of combination therapy as compared to monotherapy, lower mortality rates from several observational studies point to an advantage of combination therapies for the treatment of carbapenem resistant *Klebsiella pneumoniae* infections. Additional cohort studies also suggest that combination therapies, particularly those including a carbapenem, should be superior to monotherapies for the treatment of CRE infections.

## Plazomicin, A Next-Generation Aminoglycoside With Improved Potency

Aminoglycosides are a family of highly potent, broad-spectrum bactericidal compounds comprised of amino-modified sugar moieties. The frequently used antibiotics in this class include streptomycin, kanamycin, tobramycin, and amikacin, and they all share the structural feature of an aminocyclitol ring linked to aminosugars. Upon penetrating the bacterial outer membrane through self-promoted uptake, aminoglycosides inhibit protein synthesis by binding to the 16S rRNA of the 30S ribosomal subunit. Aminoglycosides are commonly used in the treatments of serious Gram-negative bacterial infections including *Escherichia coli,* Enterobacter, *Pseudomonas aeruginosa* and Salmonella species, and Gram-positive pathogens such as Staphylococcus and some Streptococci and Mycobacteria. Aminoglycosides are commercially available in both IV and IM formulations.

### Plazomicin Is Engineered To Be Resistant To Resistance

Plazomicin is a next-generation aminoglycoside antibiotic that Achaogen engineered to overcome key aminoglycoside resistance mechanisms. Plazomicin was developed by chemically modifying an existing aminoglycoside, sisomicin, a natural product isolated from bacteria, to shield the regions of the molecule that are targeted by the enzymes responsible for aminoglycoside resistance. Consequently, plazomicin retains activity against MDR organisms even in cases where commercially available aminoglycosides such as gentamicin and amikacin are ineffective.

Similar to carbapenem resistance, aminoglycoside resistance can develop through the following three mechanisms:

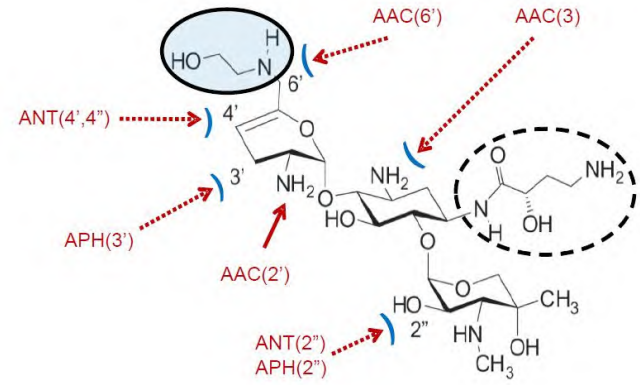
- Reduction in concentration of aminoglycoside within the cell by efflux, reduced uptake, or decreased cell permeability
- Modification of the aminoglycoside target via mutation or 16S ribosomal methyltransferases
- Production of aminoglycoside modifying enzymes

The production of aminoglycoside modifying enzymes is the most common type of aminoglycoside resistance. Reduction of bacterial cell entry by aminoglycosides only results in moderate levels of resistance and resistance through altered ribosomal binding is relatively uncommon since aminoglycosides typically bind to multiple sites on bacterial ribosomes (resistance via mutation of the aminoglycoside target is relatively uncommon because there are many copies of the gene that encodes for the rRNA target). In addition, ribosomal methyltransferases are more rare than aminoglycoside modifying enzymes. Over 100 different aminoglycoside modifying enzymes have been identified and they belong to one of the following three categories:

- N-Acetyltransferases (AAC)
- O-Adenylyltransferase (ANT)
- O-Phosphotransferases (APH)

Similar to carbapenamases, the genes that encode for aminoglycoside modifying enzymes can be transferred across bacterial species by mobile genetic elements such as plasmids and transposons. The following figure illustrates the modifications in plazomicin's structure, specifically two groups added – a hydroxyethyl group in the blue circle and a gamma-amino-alpha-hydroxybutyryl (haba) group in the dashed circle. The addition of these two groups shields regions within plazomicin that otherwise would be susceptible to aminoglycoside modifying enzymes.

The Design Of Plazomicin




Source: Achaogen; the numbers in parentheses indicate the site of modification by aminoglycoside modifying enzymes

## *In Vitro* Susceptibility Is A Reliable Indicator For Clinical Success

Antibiotic susceptibility tests measure the susceptibilities of particular bacterial strains to antimicrobial agents. The minimal inhibitory concentration (MIC) is the lowest concentration of an antibiotic that will inhibit the growth of a bacterial strain after overnight incubation. MICs are used to confirm resistance of a bacterial strain and to identify an effective dose of antibiotic. Typically, when assessing the activity of an

antibiotic, a large panel of organisms (typically at least 20 and up to thousands) of the same species are assembled. The $MIC_{50}$ is the minimum concentration of an antibiotic required to inhibit the growth of 50% of the organisms within a given panel; the $MIC_{90}$ is the minimum concentration of antibiotic required to inhibit the growth of 90% of the organisms within a given panel. MICs are determined in a laboratory setting by testing progressively lower concentrations of the antibiotic of interest on a bacterial strain in a solid growth medium or in a liquid medium. The MIC of an antibiotic is the lowest concentration of drug at which there is no observable growth.

Susceptibility test results based on MICs are typically categorized as susceptible, intermediate, resistant, sensitive-dose dependent or no interpretation. The designation of being susceptible means that the bacteria is inhibited by the plasma concentration of an antimicrobial agent with the normally recommended dose. As a result, the antimicrobial agent can be used to properly treat an infection caused by the bacteria.

A clinical retrospective cohort study concluded that actual carbapenem MICs may be more reliable in predicting clinical patient outcomes than the aforementioned categories of susceptibility to resistance (Esterly et al., *Antimicrobial Agents and Chemotherapy*, 2012). We believe this applies to other classes of antibiotics as well.

Plazomicin has demonstrated superior potency on clinical isolates of CRE as compared to other currently available antibiotics in *in vitro* assays. The following chart includes MIC data on a total of 807 clinical isolates of CRE strains.

**Superior *In Vitro* Potency Of Plazomicin On Clinical Isolates Of CRE**

| Compound | Class | N | $MIC_{50}$ (µg/ml) | $MIC_{90}$ (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/Beta-lactamase inhibitor | 731 | >128 | >128 |
| Tigecycline | Glycycline | 723 | 1 | 2 |
| Colistin/polymyxin B | Polymyxin | 692 | 1 | 4 |

Susceptible

Non-Susceptible

- N=number of strains within the overall set of 807 strains tested vs. the given antibiotic
- CLSI 2012 susceptibility criteria were used except for tigecycline and colistin, for which EUCAST 2013 criteria were used because CLSI criteria were not available
- Isolates selected had an MIC≥2 µg/mL for any type 2 carbapenem, a value defined as non-susceptible for this class according to CLSI

Source: Achaogen; N: number of clinical isolates of CRE;

## Clinical Development History

Achaogen completed one Phase II clinical trial that evaluated the efficacy and safety of plazomicin for the treatment of cUTI.

### Phase I Clinical Trials

Achaogen completed multiple Phase I clinical trials to evaluate the safety and PK profile of plazomicin and to identify the optimal dose for future clinical studies. The results from the Phase I clinical trials are summarized in the following table. The conclusion was that plazomicin was well-tolerated at doses of up to 15mg/kg for the duration that is required for the treatment of typical bacterial infections. Dose adjustment is required for patients with impaired kidney function since the majority of plazomicin is metabolized through the kidney. Importantly, a thorough QT study was completed and no cardiovascular risks were observed from the use of plazomicin.

**Summary Of Phase I Clinical Trials**

| Study No. | Objectives | Design | Plazomicin Doses | Patient No. | Key Results |
|---|---|---|---|---|---|
| 001 | Safety and PK after single and multiple doses in healthy subjects | Randomized, double-blind, placebo-controlled, parallel-group, dose escalation study | 1, 4, 7, 11, 15mg/kg IV for 3-10 days | 39 | Plazomicin was well tolerated at doses of up to 15mg/kg for 3 days |
| 003 | Safety, plasma PK and lung penetration in healthy subjects | Randomized, double-blind, placebo-controlled | Cohort 1: 15mg/kg IV for 5 days<br>Cohort 2A/2B: 10.7/15mg/kg IV, single dose | 40 | Plazomicin was well tolerated at doses of up to 15mg/kg for 5 days and penetrated into the lung |
| 004 | Safety and PK in healthy and impaired kidney function subjects | Open-label | 7.5mg/kg IV, single dose | 24 | Plazomicin's dose needs to be adjusted in patients with moderately or severely impaired kidney function |
| 006 | Thorough QT/QTc trial in healthy subjects | Randomized, double-blind, placebo and positive-controlled, crossover | 15mg/kg IV, single dose<br>20mg/kg IV, single dose | 64 (8 in part 1, 56 in part 2) | Plazomicin demonstrated no clinically relevant potential to increase risk for cardiac arrhythmias at single doses of up to 20mg/kg |

Source: Achaogen & Cowen and Company

### Phase II Clinical Trial In cUTI Met The Primary Endpoint

Plazomicin was initially being developed for cUTI and in Phase II studies demonstrated comparable microbiological and clinical efficacy to levofloxacin and a favorable safety profile. The Phase II study was a multi-national, randomized, double-blind study in cUTI and acute pyelonephritis. The trial evaluated the safety and efficacy of plazomicin at 10mg/kg or 15mg/kg as compared to an active comparator, levofloxacin (750mg), in a total of 145 patients.

Patients were randomized to receive IV plazomicin at 10mg/kg or 15mg/kg, or levofloxacin for five consecutive days. The primary endpoint of the trial was microbiological eradication rates in the modified intent to treat (mITT) population and microbiologically evaluable (ME) population at the test of cure visit (day 12). The secondary endpoint was clinical cure based on the investigator's assessment throughout the study up to day 12.

Patients were equally randomized to 10mg/kg plazomicin, 15mg/kg plazomicin, or 750mg levofloxacin during the first phase of the trial. During the second phase of the trial, the 10mg/kg treatment arm was eliminated and patients were randomized 2:1 to 15mg/kg plazomicin or levofloxacin 750mg due to patients from the two plazomicin cohorts demonstrating highly overlapping responses.

In May 2012, Achaogen announced positive results from the study. Both doses of plazomicin met the primary endpoint by demonstrating non-inferiority to levofloxacin. In microbiologically evaluable subjects, plazomicin 10mg/kg and 15mg/kg resulted in 85.7% and 88.6% eradication, respectively while levofloxacin (750mg) resulted in 81.0% eradication.

**Plazomicin Demonstrated Non-Inferiority To Levofloxacin In cUTI**

| | By-Patient Microbiological Response | Plazomicin 10mg/kg | Plazomicin 15mg/kg | Levofloxacin 750mg |
|---|---|---|---|---|
| ME | N | 7 | 35 | 21 |
| | Eradication, n (%) | 6 (85.7%) | 31 (88.6%) | 17 (81.0%) |
| | 95% CI | (42.1% - 99.6%) | (73.3% - 96.8%) | (58.1% - 94.6%) |
| | Difference (95% CI)* | | -7.6% (-31.3%, 16.0%) | |
| mITT | N | 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%) | |

* Between levofloxacin and plazomicin 15mg/kg

Source: Achaogen & Cowen and Company; ME; microbiologically evaluable; mITT: modified intent-to-treat

No serious adverse events (SAEs) attributed to plazomicin were reported. Most adverse events (AEs) were mild or moderate in severity with headache, diarrhea, dizziness, nausea and vomiting being the most frequently reported AEs and occurring in a comparable proportion of the patients from the three cohorts of the study.

A low incidence of aminoglycoside-related toxicities was observed in plazomicin-treated patients. There were two AEs, mild unilateral permanent tinnitus and mild transient vertigo, and both were considered to be related to treatment by the investigators. However, formal audiometry or vestibular testing did not reveal any clinically relevant changes in plazomicin-treated patients. There were also two AEs associated with renal dysfunction. One mild azotemia (elevation of blood urea nitrogen) was considered to be related to plazomicin treatment but one mild renal insufficiency was considered to be unrelated. Although one case of Grade 2 serum creatinine lab abnormality was recorded, the mean serum creatinine values remained stable over the five-day treatment period.

We believe that plazomicin demonstrated an overall benign safety profile in the Phase II clinical trial. The incidence of treatment-related AEs is comparable to typical aminoglycosides.

## Indication Switch Reasonable

Achaogen has since made the strategic decision to pursue serious MDR infections caused by CRE as the lead indication for plazomicin. Achaogen began discussions with the FDA regarding the CRE indication in June 2012, shortly after the positive data announcement from the Phase II clinical trial in cUTI, and eventually reached an

agreement with the agency on an SPA for the pivotal Phase III clinical trial in September 2013. Achaogen is now the ONLY antibiotic company that is specifically targeting CRE pathogens.

As we will discuss in the Competitive Landscape section of this report, many companies are developing novel antibiotics for the treatment of infections caused by Gram-negative bacteria. All other companies except Achaogen are targeting cUTI and cIAI and many are approaching near completion of pivotal Phase III testing. It would be difficult for Achaogen and plazomicin specifically to "stand out" had the company decided to pursue the same indications.

By taking advantage of plazomicin's unique strong potency against CRE pathogens to address a significantly more urgent medical need, Achaogen has successfully differentiated itself from other antibiotic developers and will be able to avoid competition once plazomicin becomes commercially available. The indication switch has also helped Achaogen secure strong support from both the FDA and the EMA, as well as from BARDA. The clinical and regulatory pathway that Achaogen is pursuing is the most efficient and low-cost option, in our opinion.

Moreover, Achaogen was able to adopt a superiority design for the pivotal Phase III clinical trial since none of the currently available treatments for CRE infections are optimal and all are associated with high mortality. We believe Achaogen will be able to implement a premium pricing for plazomicin if plazomicin demonstrates a solid survival benefit.

In summary, we believe Achaogen's decision to pursue clinical development for CRE infections is well justified with the market potential for this indication being significant and well supported by strong *in vitro* and preclinical data.

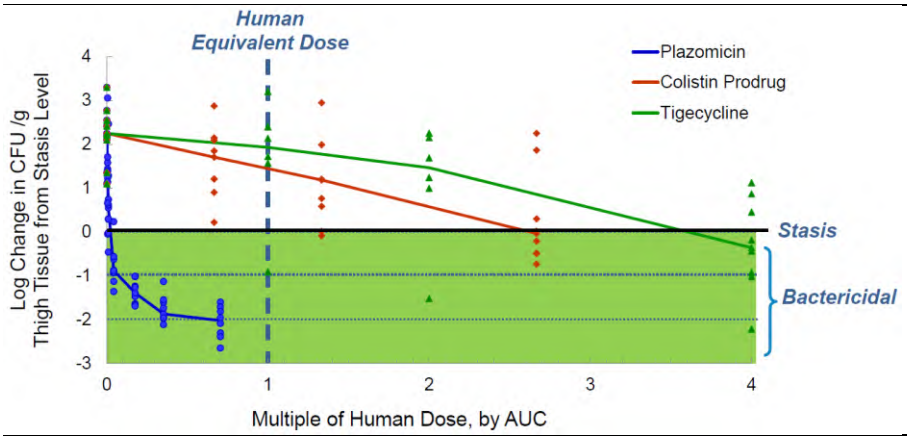
### Preclinical Study Results Provide Strong Support For Targeting CRE

The likelihood of success of the Phase III clinical trial for plazomicin in the treatment of CRE is supported by strong *in vitro* and preclinical data, in our opinion. These data have demonstrated the strong potency of plazomicin on CRE pathogens and have suggested a meaningful clinical benefit in human patients.

In a murine neutropenic thigh model, which is routinely used to evaluate the efficacy of novel antibiotics in the treatment of bacterial infections, plazomicin demonstrated much stronger bactericidal activity than both colistin and tigecycline against multiple CRE isolates. Neutropenic mice were challenged with CRE pathogens that were injected into the thighs, and the mice were then treated with plazomicin, colistin, or tigecylcine. Plazomicin was dosed in such a way as to generate plasma PK profiles similar to what QD dosing of plazomicin would generate in humans.

Bacterial bioburden measurements demonstrated that compared to colistin and tigecycline, plazomicin achieved a bactericidal effect at a much lower dose. The human equivalent dose (~4.3mg/kg/day) of the highest plazomicin dose required to achieve a one log reduction in colony forming units (CFUs, estimates of viable bacterial numbers) against any CRE strains tested in the study was much lower than the proposed human dose of 15mg/kg/day. In contrast, both colistin and tigecycline demonstrated minimal efficacy, failing to achieve a one log reduction in CFUs at a dose that is equivalent to the typical clinical dose. These data suggest the strong efficacy of plazomicin against CRE strains, particularly when compared to other antibiotics currently used for the treatment of infections caused by CRE.

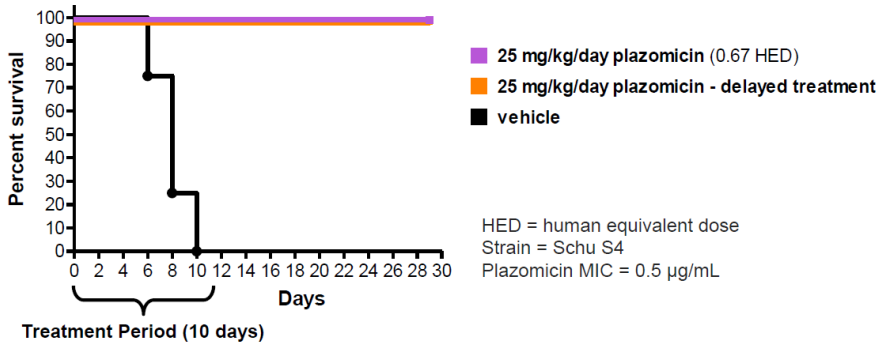
**Plazomicin Demonstrates Strong Activity In A Mouse CRE Infection Model**




Source: Achaogen; CFU: colony forming units; AUC: area under the curve

Achaogen further evaluated the efficacy of plazomicin for the treatment of lung infections in a primate pneumonic tularemia model. At a dose approximately two thirds of the human equivalent dose and even when the treatment was delayed, plazomicin treatment led to 100% survival whereas all vehicle-treated animals died within 10 days post infection.

**Plazomicin Is Efficacious In A Lethal Pneumonia Model**



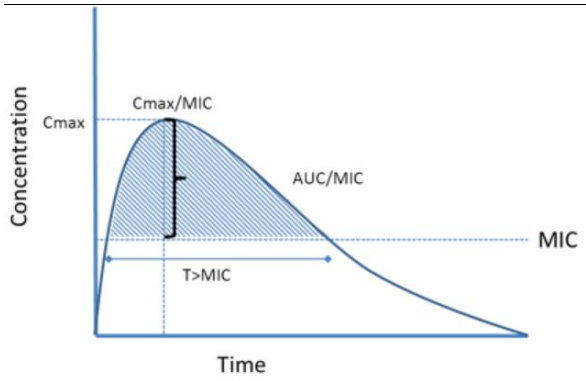

Source: Achaogen

## PK/PD Modeling Suggests Clinical Success

Achaogen further leveraged preclinical study data and computational modeling techniques to predict the clinical efficacy of plazomicin in human patients with CRE infections. Plazomicin has demonstrated strong potency against CRE strains in *in vitro* assays with favorable MIC scores. However, MIC does not provide much information about the time course of antibacterial activity required, or the concentration required *in vivo* for the successful treatment of the bacterial infection. In contrast, pharmacokinetic (PK) parameters, including peak serum level (Cmax) and the area under the serum concentration time curve (AUC), describe the time course of antibiotic serum levels but do not indicate the antibacterial potency. Combining an antibiotic's PK parameters and microbiologic activity provides the following three PK/PD parameters commonly used to predict antibiotic efficacy:

1) The ratio of maximum serum concentration to the minimum inhibitory concentration (MIC) (Cmax/MIC)
2) The ratio of the area under the plasma concentration-time curve (AUC) to MIC (AUC/MIC)
3) The duration of the dosing interval that plasma concentrations exceed the MIC (T>MIC)

**PK/PD Predictors Of Antibiotic Efficacy**




Source: Agency for Healthcare Research and Quality

Antibiotics can be divided into three groups based on their patterns of activity:

- Concentration-dependent (rate of bacterial eradication correlates with antibiotic concentration)
- Time-dependent (rate of bacterial eradication is determined by the duration of antibiotic exposure)

Each group has a different set of optimal PK/PD parameters that can be used to predict the efficacy of antibiotics within that group.

Pharmacodynamic Properties Of Antibiotics

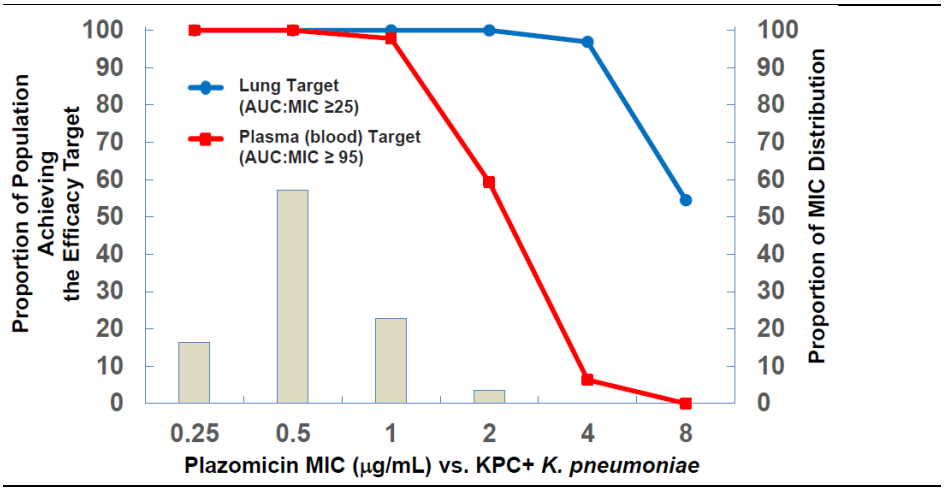
| Pattern of Activity | Sample Antibiotics | Goal of Therapy | PK/PD Parameter |
|---|---|---|---|
| **Type I** | | | |
| Concentration-dependent killing and prolonged persistent effects | Aminoglycosides<br>Fluoroquinolones<br>Glycopeptides/lipopeptides<br>Telithromycin | Maximize concentrations | 24h-AUC/MIC<br>Cmax/MIC |
| **Type II** | | | |
| Time-dependent killing and minimal persistent effects | β-lactams<br>Macrolides<br>Oxazolidinones<br>Tetracyclines<br>Vancomycin | Maximize duration of exposure | T>MIC |

Source: Cowen and Company; adapted from www.rxkinetics. com

Aminoglycosides are concentration-dependent antibiotics that demonstrate increasingly higher bactericidal activity as their concentrations at the site of infection increase, up to a limit of perhaps 10 times the MIC for the organism. For antibiotics exhibiting this type of profile, drug concentrations, and not exposure time, are best correlated with bacterial eradication. It has also been demonstrated that clinical responses can be reliably predicted by measuring the ratio between the antibiotic's AUC and MIC. To achieve desirable efficacy, this ratio is expected to be above a certain threshold, depending on the type and severity of the infection.

Preclinical studies that Achaogen has completed using plazomicin in murine models suggest that a AUC:MIC ratio of ≥95 in bloodstream infections and a ratio of ≥25 in lung infections would predict strong antibiotic treatment efficacy. The following chart represents Achaogen's projection of plazomicin's clinical efficacy in human patients when a total of 373 PKC-producing *Klebsiella pneumoniae* isolates were evaluated. The projection was performed by comparing AUC:MIC ratios in patients to the susceptibility of CRE isolates. As the gray bars and the Y-axis on the right hand side suggest, plazomicin demonstrated strong potency against the vast majority of the isolates with an MIC of ≤1. The red and blue lines suggest that at these MIC scores, plazomicin at 15mg/kg (the dose to be used in the pivotal Phase III clinical trial) would be predicted to demonstrate strong efficacy in close to 100% of both bloodstream infection and lung infection patients.

Projection Of Strong Plazomicin Clinical Efficacy




Source: Achaogen

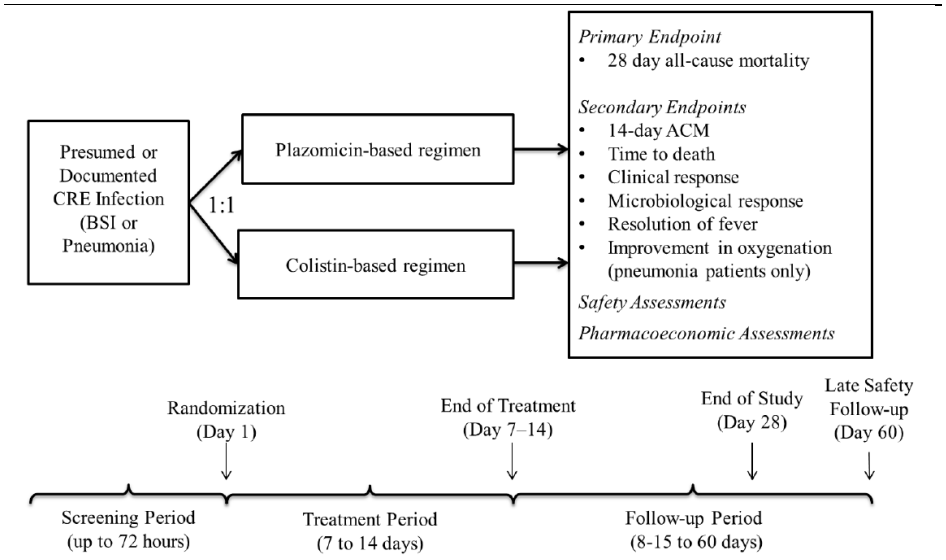
## The Ongoing Phase III Study Aims To Demonstrate Superiority

Achaogen initiated the Phase III clinical trial in 1Q14. The randomized, open-label study is designed to demonstrate the superiority of plazomicin as compared to colistin, when combined with a second antibiotic, for the treatment of bloodstream infections or hospital-acquired pneumonia caused by CRE. The study will enroll approximately 360 patients with presumed or confirmed CRE infections – whose infections are caused by pathogens either presumed or confirmed to have an MIC of ≥ 4μg/mL for meropenem.

Patients will be equally randomized to receive seven to 14 days of repeated IV infusions of either plazomicin or colistin, each in combination with a second adjunct antibiotic therapy, which can be either meropenem or tigecycline based on the investigator's choice. Patients randomized into the colistin cohort will receive a loading dose, followed by subsequent dose at every eight or 12 hours. Achaogen has not disclosed the specific colistin dose to be used in the pivotal Phase III study but commented that it is based on the most recent PK/PD studies on the drug and is line with the standard dose being used in the two large academic studies in Europe and the U.S. The plazomicin dose will be adjusted based on each individual patient's condition and will be capped at 15mg/kg per administration. Patients who require higher doses will receive multiple administrations per day at lower doses.

The primary endpoint of the study is all-cause mortality at day 28, consistent with what the current FDA guidelines recommend as the efficacy endpoint for HAP/VAP. Secondary endpoints include time to death through 28 days, all-cause mortality at 14 days, clinical response rates at the end of treatment (14 days), at test of cure (21 days), at the end of study (28 days), safety, and PK parameters.

Phase III Clinical Trial Design




Source: Achaogen

## Meta-Analysis Suggests A High Likelihood Of Success

The pivotal Phase III clinical trial of plazomicin is powered at 70% to demonstrate an absolute reduction of 12% (from 35% to 23%) in 28-day all-cause mortality. This design is based on a meta-analysis that Achaogen conducted, based on both published and unpublished observational data, on the mortality in patients with bloodstream infections caused by carbapenamase-producing Enterobacteriacea.

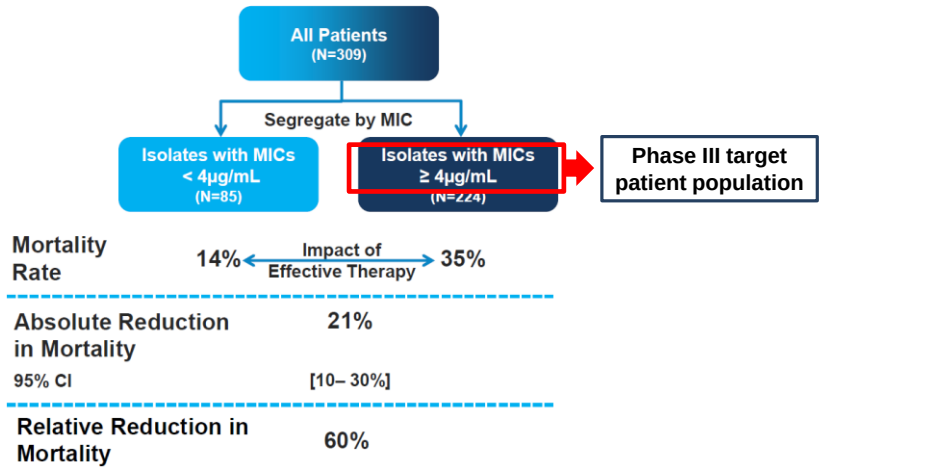
The meta-analysis included a total of 309 patients. The patients were divided into two groups based on the MICs of their isolates against type 2 carbapenems such as meropenem or imipenem:

1) 224 patients had isolates with a carbapenem MIC of ≥ 4μg/mL and received ANY type of combination therapy

2) 85 patients had isolates with a carbapenem MIC of < 4μg/mL and received combination therapy that included a carbapenem (the production of carbapenamase does not necessarily lead to carbapenem resistance)

The meta-analysis revealed that the mortality rate in patients with carbapenem-resistant pathogens (MIC ≥ 4μg/mL) was 35% with currently available therapy whereas the mortality rate was only 14% when the pathogens were fully or partially susceptible to carbapenems and a carbapenem was included in therapy. This is equal to an absolute reduction in mortality of 21% when effective antibiotics are used for treatment.

**Meta-Analysis Of Mortality In Patients With CPE Bloodstream Infections**




Source: Achaogen; CPE: carbapenamase-producing Enterobacteriacea

Achaogen's pivotal Phase III clinical trial of plazomicin will enroll the same patient population with CRE infections who demonstrated a 35% mortality rate when receiving currently available treatments most frequently comprised of colistin. Therefore, we believe it is reasonable to expect a comparable mortality rate from the colistin treatment cohort in the Phase III study.

Patients enrolled in the plazomicin treatment cohort of Achaogen's Phase III study, by having the same CRE pathogens with an MIC ≥ 4µg/mL, are slightly different from those who demonstrated a 14% mortality rate in the meta-analysis. However, we believe it is possible to draw an analogy since plazomicin has demonstrated strong potency in CRE pathogens with an MIC well below 4µg/mL. As a result, we believe that the 23% target mortality that Achaogen has set for the plazomicin-treated patients in the Phase III clinical trial is quite conservative. Based on the strong data from the *in vitro* and preclinical studies that Achaogen has completed, we expect plazomicin to demonstrate better clinical benefit in the pivotal Phase III study.

The powering of the pivotal Phase III clinical trial at 70% is below that of a typical Phase III study. However, we do not believe this is an issue for the following reasons:

1) The design of the pivotal study to demonstrate an absolute reduction of 12% in mortality is conservative as compared to the 21% reduction observed in the meta-analysis. If plazomicin performs as well as the *in vitro* MIC numbers would suggest, we could expect a higher clinical benefit with lower mortality.

2) Achaogen has reached an agreement with the FDA on an SPA for the design and analysis of the pivotal study. A higher powering would require more patients to be enrolled and will further prolong the duration of the study. We believe the FDA has clear recognition of the unmet medical need for a safe and efficacious therapy for the treatment of CRE infections. We also believe that the Agency may demonstrate additional flexibility in reviewing the clinical data from the pivotal study.

## Enrollment Criteria Target Optimal Patient Population To Maximize Clinical Benefit

Achaogen will utilize the APACHE II (Acute Physiology and Chronic Health Evaluation II) score to screen for patients who have the highest possibility of demonstrating a clinical benefit with plazomicin treatment. The APACHE II score is a classification system based on disease severity that can be used to project ICU mortality based on a number of laboratory values and patient signs and taking into account both the patient's acute and chronic disease. The measurement is conducted within 24 hours after patient admission to the ICU and an integer score from 0 to 71 is generated based on the measurements. A higher score suggests a higher disease severity and a higher risk of death.

For the ongoing Phase III study, Achaogen will enroll patients with APACHE II scores of between 15 and 30 (both inclusive). This range will help Achaogen exclude patients who either are not likely to die even without effective antibacterial treatment (APACHE II score <15) or likely to die even with effective antibacterial treatment (APACHE II score >30). Thus, the target patient population is enriched for those whose mortality will most likely be impacted through administration of an effective antibiotic and as a result, the possibility of plazomicin demonstrating a clinical benefit is maximized.

Patients will undergo a screening period of 72 hours, during which their pathogens will be tested for carbapenem resistance. Either presumptive identification of CRE with a rapid testing method from an appropriate culture specimen, or definitive identification with susceptibility testing conducted at a local laboratory, will qualify the patient to be enrolled into the study. Isolates from all patients will eventually be confirmed for carbapenem resistance through central laboratory testing and the primary analysis population will be the patients with isolates that are confirmed by central lab to have MICs ≥4μg/mL. Patients who have received greater than 72 hours of empirical antibiotic therapy or who have CRE isolates with reduced susceptibility to colistin will be excluded from the study, among other exclusion criteria.

We believe the overall enrollment criteria of the Phase III study maximizes both the number of patients to be enrolled and the chances of success for plazomicin.

## Two Studies Planned In Parallel With The Phase III

Additionally, Achaogen plans to initiate a single-arm, open-label, supportive efficacy study in patients with serious CRE infections by year-end 2014 and to report top-line data in 4Q15. The company has not disclosed the specific design of the study except that approximately 50 patients with serious CRE infections will be enrolled. We believe Achaogen will likely target a slightly different patient population form those who would qualify for the pivotal Phase III study to avoid generating a negative impact on patient enrollment in the pivotal study.

Achaogen additionally plans to initiate a non-randomized safety study after the first interim analysis in 2H15 to expand the safety database that will be required for global regulatory approval (300 patients). The patients to be enrolled into the safety study will include those who are not eligible for the pivotal Phase III study so we do not expect the safety study to have any impact on the pivotal study enrollment.

Plazomicin Phase III Clinical Development Program Summary

| Type | Objectives | Planned Enrollment | Patients on Plazomicin | Initiation | Top-line Data |
|---|---|---|---|---|---|
| Pivotal Phase III | Primary endpoint: Superiority to colistin with respect to all-cause mortality at 28 days in patients with serious CRE infections<br>Secondary endpoint: Safety, PK | 360 | 180 | 1Q14 | 1H17 |
| Supportive Efficacy | Safety and efficacy of plazomicin in patients with serious CRE infections | 50 | 50 | 4Q14 | 4Q15 |
| Safety | Safety of plazomicin in patients with serious CRE infections | 70 | 70 | 2H15 | 1H17 |
| | **Number of patients required for the safety database** | | **300** | | |

Source: Achaogen & Cowen and Company

## Individual Patient Dosing Optimization With Therapeutic Drug Management (TDM)

Achaogen has developed a plazomicin-specific assay to be used in the Therapeutic Drug Management (TDM) to quantitatively measure plasma concentrations of plazomicin so that dose adjustment is possible to optimize drug exposure in each patient. The assay was developed in collaboration with ARK Diagnostics; a private company based in Fremont, CA, and has been approved by the FDA for use in the Phase III clinical trial. The use of TDM in the Phase III clinical trial will help ensure that every patient's serum exposure to plazomicin is within an acceptable range of the target mean steady-state area under the curve (AUC). The technology used in the assay is similar to what is being used for other aminoglycosides and Achaogen plans to conduct the clinical performance evaluation, which is required for the FDA to approve the assay, in parallel with the Phase III clinical trial. The use of TDM in the Phase III clinical trial, by individualizing treatment for each patient, will enhance the possibility of success, in our opinion.

Achaogen entered into a development service agreement with ARK Diagnostics in 2003. In addition to the co-development activities, the agreement included core terms that entitled ARK to the first right to commercialize the assay in the U.S. and the EU and to manufacture and supply the assay worldwide for commercialization. We believe that Achaogen could potentially develop the assay into a product to be bundled with plazomicin and that it will enhance the uptake of plazomicin by the physician community.

## Clinical Development Risk Of Plazomicin

The MIC score, although a reliable indicator of an antibiotic's potency against an organism, is only one of many factors that determine the ultimate clinical outcome of treatment. Other factors to be taken into account include protein binding of the antibiotic, pharmacokinetics, distribution into the site of infection, the adequacy of the patient's host defenses, and the amount of antibiotic exposure an organism requires for its eradication. Achaogen has never conducted a clinical study of plazomicin for the indication of CRE infection so clinical data is lacking to support plazomicin's efficacy for this indication in human subjects with CRE infection.

Another risk is associated with the safety profile of plazomicin in sicker patients in the Phase III clinical trial, particularly in patients with compromised renal function. The

completed Phase II clinical trial in cUTI reported two renal function-related AEs: one mild azotemia deemed related to plazomicin treatment and one acute renal insufficiency considered unrelated. The pivotal Phase III clinical trial will exclude patients in acute renal failure or on intermittent hemodialysis (IHD) at the time of screening. However, given the difference in disease severity between cUTI patients and patients with bloodstream and nosocomial pneumonia, it can be expected that the incidences of both overall AEs and renal AEs could be higher.

## Competitive Landscape

Several companies are now engaged in the development of antibiotics for the treatment of infections caused by Gram-negative pathogens. Overall, the Gram-negative market is less crowded than the Gram-positive market and our physician consultant believes it is a landscape where treatment algorithms are not as well established.

The FDA provided early guidance on its new objective efficacy endpoints for cUTI and cIAI infections to encourage development of new drugs against resistant Gram-negative strains, although mortality benefit trials remain a requirement for a nosocomial pneumonia indication. We estimate the global market opportunity for new anti-infective agents with potent activity against a broad spectrum of MDR Gram-negative pathogens could be larger than the current market opportunity for anti-infectives targeting MRSA Gram-positive pathogens.

Achaogen is the ONLY company conducting clinical trials specifically for CRE pathogens. The unique pathogen-targeted approach and the selection of CRE infections instead of other common Gram-negative infections as the lead indication will help Achaogen effectively avoid competition, in our opinion.

### The Medicines Company

In December 2012, The Medicines Company acquired Rempex, a private company focused on the discovery and development of novel antibacterial drugs. With the acquisition The Medicines Company gained rights to Carbavance, the combination of a novel broad-spectrum β-lactamase inhibitor (RPX7009) and an undisclosed marketed carbapenem. Rempex completed a Phase I dose-escalation study of Carbavance in normal subjects, and The Medicines Company expects to initiate registration studies in 2014.

Carbavance could be a potential major competitor to plazomicin among all other drug candidates being developed for Gram-negative bacterial pathogens. RPX7009 is potent against KPC and the Phase I study completed by Rempex reportedly demonstrated both a strong PK and safety profile. Although the planned registration studies will be for the indication of cUTI, The Medicines Company does plan to conduct a small study for CRE in patients with multiple infection types for potential future label expansion.

However, RPX7009 has no activity against two other classes of carbapenemases metallo-β-lactamases and oxacillinases. In addition to no clinical data from Phase II studies to support the efficacy and safety in patients with actual bacterial infections, the CRE study will only be descriptive and is not designed to demonstrate superiority over currently available therapies. Finally, based on the disclosed clinical development timeline, we expect at least a three- to four-year delay before Carbavance receives label expansion for CRE after plazomicin's entry into the market. Therefore, we are

optimistic that plazomicin should have sufficient time to establish dominance before facing any meaningful competition and that plazomicin's clinical profile should be strong enough to fend off any Carbavance challenge.

### Tetraphase Pharmaceuticals

Tetraphase is developing a portfolio of tetracycline derivatives designed for broad spectrum coverage against resistant bacteria, including MDR gram-negative pathogens. Tetraphase's lead candidate is eravacycline, a potent broad spectrum IV administered and potentially oral, tetracycline antibiotic with activity against Gram-positive and Gram-negative strains, currently in Phase III IGNITE (**I**nvestigating **G**ram-**n**egative **I**nfections **T**reated with **E**ravacycline) development. In July 2013, the FDA granted eravacycline QIDP designation for both cUTI and cIAI.

In September 2012, Tetraphase reported positive results from a 143-patient, Phase II trial comparing IV eravacycline to ertapenem in cIAI patients. Eravacycline achieved infection cure rates (at 10 to 14 days) comparable to ertapenem and a strong safety profile with low rates of gastrointestinal side effects. In August 2013, Tetraphase initiated the Phase III clinical trial of eravacycline for the treatment of cIAI. Subsequently in March 2014, Tetraphase announced that patient enrollment had begun in the Phase III IV-to-oral clinical trial of eravacycline for the treatment of cUTI. The randomized, multi-center, double-blind Phase III study will evaluate the efficacy and safety of eravacycline compared with levofloxacin in the treatment of cUTI. Tetraphase expects to report top-line data from the two Phase III studies in 1Q15 and mid-2015, respectively, and to file for U.S. regulatory approval for both indications by the end of 2015.

### Forest Laboratories / AstraZeneca

In December 2009, Forest Laboratories acquired full U.S. rights to Novexel's novel β-lactamase inhibitor avibactam (NXL-104), following AstraZeneca's acquisition of Novexel. Avibactam prevents the development of extended-spectrum β-lactamases (ESBLs) which is a common mechanism of resistance to β-lactam antibiotics in Gram-negative pathogens. Forest also acquired global rights to the Teflaro/avibactam combination (in Phase I trials) and U.S. and Canadian rights to Novexel's CAZ-104 (IV ceftazidime/avibactam combination). Forest subsequently out-licensed international rights to the Teflaro/NXL-104 combination to AstraZeneca in return for a royalty on AstraZeneca's international sales and elimination of Forest's royalty and milestone obligations on U.S. sales.

Ceftazidime/avibactam's spectrum of activity covers resistant Gram-negative infections, including coverage for *Pseudomonas aeruginosa* strains, and Forest has completed Phase II trials in both cIAI and cUTI. The Phase II trial in cUTI compared the efficacy and safety of IV ceftazidime/avibactam versus imipenem/cilastatin for the treatment of hospital acquired cUTI with Gram-negative pathogens in a total of 137 patients. The results from the trial demonstrated comparable microbiological response rates from two groups at the test-of-cure evaluation five to nine days after the final treatment in the microbiologically evaluable patient population. In patients with any of the seven ceftazidime-resistant pathogens that were isolated in the study, the favorable response rate was 85.7%, indicating good efficacy of the avibactam component. Forest also completed a Phase II trial in cIAI which compared the efficacy and safety of IV ceftazidime/avibactam plus metronidazole to meropenem. The trial reported similar positive data with a comparable proportion of microbiologically evaluable patients from both groups achieving a favorable clinical response. In those

patients with ceftazidime-resistant isolates, the ceftazidime/avibactam/metronidazole favorable clinical response rate was 96.2%.

Forest and AstraZeneca are conducting multiple Phase III clinical trials to evaluate the ceftazidime/avibactam combination for the treatment of cUTI and cIAI. Top-line data are expected in mid-2014.

### Cubist Pharmaceuticals

In December 2009, Cubist acquired Calixa Therapeutics and its lead anti-infective candidate CXA-201, an IV combination of Calixa's novel broad-spectrum cephalosporin ceftolozane (CXA-101) and the β-lactamase inhibitor tazobactam (a component of Pfizer's Zosyn). Cubist acquired the rights to develop and commercialize ceftolozane/tazobactam, and other products that incorporate ceftolozane, in all territories of the world except select Asian-Pacific territories.

CXA-201 has demonstrated potent *in vitro* activity against resistant *Pseudomonas aeruginosa* strains. Cubist initiated the first Phase III trial in patients with cUTI in July 2011 and announced positive results in November 2013. CXA-201 met the primary endpoint of statistical non-inferiority compared to levofloxacin in a composite of microbiological eradication and clinical cure rate at the test of cure visit. Cubist initiated two additional Phase III trials in December 2011, testing CXA-201 in hospitalized patients with cIAI. In December 2013, Cubist announced positive top-line results and CXA-201 met the FDA and the EMA defined primary endpoints of statistical non-inferiority compared to meropenem. Based on the positive data from the two Phase III clinical trials, Cubist expects to submit an NDA in 1H14 and an MAA in 2H14 for both cUTI and cIAI.

Cubist is also developing CXA-201 for the treatment of HAP/VAP and the drug candidate was granted Fast Track Designation for this indication in May 2013. Cubist plans to initiate a Phase III trial of CXA-201 in HAP/VAP in 1H14 to demonstrate non-inferiority to imipenem in 28-day mortality rates.

### Melinta Therapeutics

Melinta Therapeutics has RX-O4, a rational drug design system using a discrete, novel binding site within the ribosome to develop new classes of antibiotics. Melinta has partnered with Sanofi on the program and the RX-04 series of antibiotics are designed to treat multi-drug resistant Gram-positive (including MRSA) and Gram-negative (*Klebsiella pneumoniae*, *Acinobacter baumannii*, *Pseudomonas aeuroginosa*, and *Escherichia coli*) infections. Preclinical studies demonstrated the efficacy of sample compounds from each of three novel classes of protein synthesis inhibitors.

Competitors In Late Stage Clinical Development

| Drug Candidate | Company | Stage | Coverage KPC | Coverage MBL | CRE Focus | Indications |
|---|---|---|---|---|---|---|
| Plazomicin | Achaogen | PIII | + | + | + | CRE in BSI & HAP/VAP |
| Carbavance | The Medicines Company | PIII planned for 2014 | + | – | + | cUTI & others |
| Eravacycline | Tetraphase | PIII | + | + | – | cUTI & cIAI |
| CAZ-104 | Forest & AstraZeneca | PIII | + | – | – | cUTI, cIAI & HAP/VAP |
| CVA-201 | Cubist | PIII | – | – | – | cUTI, cIAI & HAP/VAP |

Source: Achaogen, & Cowen and Company;

## Premium Pricing Based On Pharmacoeconomic Analysis

Nosocomial infections are a major contributor to the total health and economic burden both in the U.S. and globally. Blood stream infections and pneumonia, the two indications targeted by Achaogen in the Phase III clinical trial for plazomicin, constitute the majority of the hospital-associated infections affecting a total of 1.7 million patients at a rate of one in every 20 hospitalizations per year. The infections impact patients' lives and impose substantial clinical and economical costs of up to $9.8 billion annually. In cases involving invasive surgery, the mean length of stay is approximately 11 days costing $32,900 for sepsis, and 14 days at a cost of $46,400 for pneumonia. Since most CRE infected patients are in acute healthcare settings such as ICUs, the cost of treatment is expected to be greater. Moreover, there is significant invisible cost added to patients and their families.

Pharmacoeconomic analyses justify a premium pricing for plazomicin if the drug candidate successfully achieves the primary endpoint in the pivotal Phase III study by demonstrating a statistical significant reduction in mortality in CRE infected patients.

## Antipseudomonal Program And A Strong Discovery Engine

### MDR *Pseudomonas aeruginosa*: Also A Significant Threat

Enterobacter, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, along with *Enterococcus faecium*, are often referred to as ESKAPE pathogens because they escape the impact of antibiotics. Multi-drug resistant (MDR) pseudomonas pathogens are becoming an increasing threat for the most common hospital-acquired infections, including nosocomial pneumonia, cUTI, and cIAI. MDR *Pseudomonas aeruginosa* is responsible for approximately 13% or 6,700 infections out of the 51,000 total Pseudomonas infections that occur annually. Some strains are resistant to nearly all classes of antibiotics including aminoglycosides, cephalosporins, fluoroquinolones and carbapenems. Therefore, *Pseudomonas aeruginosa* infections are associated with high rates of morbidity and mortality. Moreover, MDR resistant Pseudomonas is a global problem, as compared to MRSA infections which are generally limited to North America. Our clinical consultants are concerned that leading Gram-negative antibiotics are showing Pseudomonal resistance rates of 15% to 25%, leaving little to no options for treating MDR strains.

Achaogen has two additional programs that target infections caused by *Pseudomonas aeruginosa*. The first program seeks to discover and develop small molecule inhibitors of LpxC, an enzyme that is essential for the synthesis of the outer membrane of Gram-negative bacteria. The second program is a therapeutic antibody.

ACHN-975 was an earlier product candidate from the LpxC inhibitor development program. Achaogen filed an IND with the FDA in 1Q12 and dosed the first patient in May 2012 in a Phase I randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of single ascending dose of ACHN-975 in healthy volunteers. The study was funded under a contract award to Achaogen by the Defense Medical Research and Development Program. A second Phase I study of multiple ascending doses of ACHN-975 administered for up to 14 days was subsequently initiated, but later terminated due to inflammation at the infusion site in some of the subjects.

In addition to the ongoing Phase III and preclinical programs, Achaogen is actively engaged in the discovery and identification of novel antibiotic candidates for difficult-to-treat bacterial infections. Achaogen's approach combines the company's expertise in both biology and chemistry, which we believe will support the company's long-term growth.

## Intellectual Property

Achaogen maintains global rights to plazomicin. The U.S. Composition of Matter patent that covers this drug candidate (U.S. Patent No.8,383,596; "*Antibacterial aminoglycoside analogs*) provides strong protection through June 2031, including 923 days of patent term adjustment. Upon regulatory approval, and depending on the date of such approval, plazomicin will further be entitled to up to five years of patent term extension based on the Hatch-Waxman Act. Achaogen has built a comprehensive patent family for plazomicin, which includes one pending U.S. patent application and 14 corresponding foreign patents and patent applications, in addition to the above issued U.S. patent.

In January 2006, Achaogen entered into a license agreement with Isis Pharmaceuticals for certain aminoglycoside compounds and related know-how for clinical development and commercialization. The agreement requires Achaogen to pay Isis $4.0 million upon dosing the first patient in the Phase III trial of plazomicin, and up to $9.75 million for the second aminoglycoside product developed under this agreement. The total payment to Isis upon the achievement of specified development and regulatory milestones relating to plazomicin is up to $19.5 million, of which $7 million will have been paid in total upon payment of the $4 million Phase III initiation milestone.

Achaogen's patent portfolio for the LpxC inhibitor compounds is comprised of seven patent families that include U.S. and international patent applications as well as issued U.S. patents that Achaogen in-licensed from the University of Washington. The expiration dates range from 2024 to 2034.

## Achaogen Has Secured Sufficient Capital For Phase III Study Completion

In March 2014, Achaogen completed an initial public offering and raised a total of $82.8 million in gross proceeds. The company had cash and cash equivalents of $10.7 million as of year-end 2013. Achaogen expects to use approximately $35 million to $40 million of net proceeds from the offering, in combination with the expected funding of approximately $60 million from the BARDA contract, to support plazomicin's

registration program. The BARDA contract contains an unexercised option for additional funding to provide further support for plazomicin's registrational studies. We believe Achaogen's current balance sheet will be sufficient to fund the clinical development of plazomicin through top-line data readout from the pivotal Phase III clinical trial.

## Financial Analysis Suggests That Shares Are Undervalued

We ascertain the value of Achaogen shares by employing four different methodologies. First, we utilize a discounted earnings model whereby the first year of meaningful EPS is discounted back to 12 months from the present. We apply a PE multiple that is in line with the mean multiple of the profitable biotech companies and employ a discount rate that takes into account clinical, regulatory and commercialization risk. Our model assumes profitability in 2019, with a fully diluted estimated EPS of $1.52. However, we base our valuation on the estimated EPS of $3.24 in 2020 since that will be the first year Achaogen will book full-year worldwide sales and royalty revenue. We then apply a 25x multiple that is in line with the forecasted industry average in 2014. Based on the risk associated with an investment in Achaogen, we discount back 25% and arrive at what we believe to be a fair 12-month target price.

**Achaogen, Inc. Discounted Earnings Model**

| 2020E EPS | |
|---|---|
| Diluted | $3.24 |
| PE | 25 |
| Discount Years | 5.70 |
| Discount Rate | 25.0% |
| Valuation | $22.68 |

| Forward P/E Ratio | Discount Rate | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 55.0% | 50.0% | 45.0% | 40.0% | 35.0% | 30.0% | 25.0% | 20.0% |
| 15x | $ 3.99 | $ 4.81 | $ 5.84 | $ 7.13 | $ 8.78 | $ 10.88 | $ 13.61 | $ 17.17 |
| 20x | 5.32 | 6.42 | 7.79 | 9.51 | 11.70 | 14.51 | 18.14 | 22.90 |
| 25x | 6.66 | 8.02 | 9.73 | 11.89 | 14.63 | 18.14 | 22.68 | 28.62 |
| 30x | 7.99 | 9.63 | 11.68 | 14.27 | 17.55 | 21.76 | 27.22 | 34.35 |
| 35x | 9.32 | 11.23 | 13.63 | 16.64 | 20.48 | 25.39 | 31.75 | 40.07 |
| 40x | 10.65 | 12.84 | 15.57 | 19.02 | 23.40 | 29.02 | 36.29 | 45.80 |
| 45x | 11.98 | 14.44 | 17.52 | 21.40 | 26.33 | 32.65 | 40.83 | 51.52 |
| 50x | 13.31 | 16.05 | 19.47 | 23.78 | 29.25 | 36.27 | 45.36 | 57.25 |
| 55x | 14.64 | 17.65 | 21.41 | 26.15 | 32.18 | 39.90 | 49.90 | 62.97 |

Source: Cowen and Company

We then use a discounted cash flow (DCF) model to discount the estimated future cash flow booked by Achaogen to arrive at the calculated present value of the company's shares. From our revenue buildup model, we estimate the final year cash flow of $238 million to the company in 2025. We apply an industry standard discount rate of 12% but apply a conservative perpetual growth rate of -5% given the potential competition in out years.

Achaogen, Inc. Discounted Cash Flow Model

| | |
|---|---|
| Final year FCF | 238 |
| Perpetual Growth Rate | -5.0% |
| **Terminal Value** | **1,328** |
| Discount Factor | 0.26 |
| **Present Value of Terminal Value** | **351** |
| **Present Value of Cash Flows** | **343** |
| **Enterprise Value** | **694** |
| Add: Net cash | 80 |
| **Market Value** | **774** |
| Fully Diluted Shares Outstanding | 18.6 |
| **Value per Fully Diluted Share** | **$41.62** |
| *Possibility of success* | *50%* |
| **Risk aAdjusted Value per Fully Diluted Share** | **$20.81** |

Source: Cowen and Company

We further determine the value of Achaogen shares by using a clinical net present value (NPV) model based on the peak U.S. sales revenue in the year 2025, the out-year of our revenue buildup model. We estimate a peak market penetration of 25% for plazomicin and our projected 2025 revenue is approximately $415.1million in the U.S. and $278.9 million from rest of world. In both our DCF and clinical NPV models, we assign a success probability of 50% based on the safety and clinical efficacy of plazomicin as well as the current clinical development stage. We employ 100% for the overall economics from the U.S. market, based on the projection that Achaogen will commercialize plazomicin independently in the U.S., and a 15% royalty rate from ex-U.S. territories. Taking into account the number of current shares outstanding, we obtain a total clinical NPV of $22.78.

Achaogen, Inc. Clinical Net Present Value Model

| Drug name | Indication | Status | Launch | Success | Peak Sales (US$m) | Economics | Profitability | NPV (US$) |
|---|---|---|---|---|---|---|---|---|
| Plazomicin U.S. | CRE | Phase III | 2018 | 50% | 415.1 | 100% | 85% | 20.4 |
| Plazomicin ex-U.S. | CRE | Phase III | 2019 | 50% | 278.9 | 15% | 100% | 2.4 |
| | | | | | | | Total | 22.78 |

Source: Cowen and Company

## Achaogen's Valuation: What History Would Say

In July 2013, Cubist announced the decision to acquire both Trius Therapeutics and Optimer Pharmaceuticals for $818 million and $801 million, respectively. Trius has completed two Phase III trials for the oxazolidinone, tedezolid, and filed an NDA with the FDA. Optimer was marketing fidaxomicin (Dificid) in collaboration with Cubist. Net sales were $35.8 million in 1H and reported by Cubist to be $15.8 million in 4Q13.

Cubist's acquisition of Trius and Optimer reminded the Street of a strong wave of M&A activity that took place in the antibiotics space approximately 10 years ago, when Vicuron was acquired by Pfizer in June 2005 for $1.9 billion. Pfizer shelved the lipoglycopeptide dalbavancin as the FDA was still not clear at the time on what the proper endpoints should be for acute bacterial skin and skin structure infections (ABSSSI) and the echinocandin anidulafungin was launched under the name Eraxis. Shortly prior to this, Peninsula Pharmaceuticals was acquired by Johnson & Johnson in April 2005 for $245 million. The company was acquired for doripenem, an IV carbapenem that was launched under the name Doribax for cUTI and cIAI.

When Peninsula was acquired, the company spun out a 5th generation IV cephalosporin into a newco, Cerexa Inc. Cerexa was acquired in January 2007 by Forest Labs for $493.6 million. The lead drug that precipitated the acquisition was ceftaroline, now marketed as Teflaro by Forest for CABP and ABSSSI. The 2013 sales for ceftaroline were $44 million and Forest has guided for $60 million in sales in 2014.

Cempra, Durata and Tetraphase completed IPOs in 2012 and 2013, respectively and all companies have late stage candidates for the treatment of either Gram-positive or Gram-negative bacterial infections.

The mean take-out value/market cap of the companies listed above is currently $593 million and Achaogen is trading at a market cap of $240 million. Given the 60% discount Achaogen shares are currently trading in relation to the mean of the above mentioned take-out valuations and market caps, we believe this name is an ideal investment for investors looking for strong fundamentals, a clean capital structure and a strong technology base.

**Achaogen, Inc. Comparative Company Analysis**

| Company | Type | Lead Indication | Phase | Action | Valuation/Market Cap |
|---|---|---|---|---|---|
| Trius Therapeutics | Public | ABSSSI | NDA | Acquired by CBST | $818.00 |
| Optimer Pharmaceuticals | Public | CDAD | Approved | Acquired by CBST | $801.00 |
| Cerexa, Inc. | Private | CABP and ABSSSI | Approved | Acquired by FRX | $493.60 |
| Vicuron Pharmaceuticals | Public | ABSSSI | III | Acquired by PFE | $1,900.00 |
| Peninsula Pharmaceuticals | Private | Complicated UTI and IAI | III | Acquired by JNJ | $245.00 |
| Rempex Pharmaceuticals | Private | Gram - indications | I | Acquired by MDCO | $140.00 |
| Durata Therapeutics | Public | ABSSSI | NDA | 2012 IPO | $329.60 |
| Cempra | Public | CABP and PJIs | III | 2012 IPO | $352.32 |
| Tetraphase Pharmaceuticals | Public | Complicated UTI and IAI | III | 2013 IPO | $256.20 |
| **Mean of Group** | | | | | **$592.86** |
| **Achaogen** | **Public** | **Serious CRE infections** | **III** | **2014 IPO** | **$239.75** |

Coverage at Cowen and Company: CEMP is covered by Edward Nash with an Outperform rating

Source: Cowen and Company. CEMP $10.60 as of 4/7/14.

## Achaogen, Inc. Revenue Buildup Model

| | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E |
|---|---|---|---|---|---|---|---|---|
| **Plazomicin for Carbapenem-Resistant Enterobacterioceae (CRE)** | | | | | | | | |
| **U.S.** | | | | | | | | |
| Annual number of hospitalizations (MM) | 36.0 | 36.4 | 36.7 | 37.1 | 37.5 | 37.8 | 38.2 | 38.6 |
| *% of hospitalized patients who are infected with pneumonia* | *0.8%* | *0.8%* | *0.8%* | *0.8%* | *0.8%* | *0.8%* | *0.8%* | *0.8%* |
| Number of patients infected with nosocomial pneumonia (NP) (MM) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| *% of hospitalized patients who are infected with bloodstream infections* | *0.6%* | *0.6%* | *0.6%* | *0.6%* | *0.6%* | *0.6%* | *0.6%* | *0.6%* |
| Number of patients infected with bloodstream infections (BSI) (MM) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Total number of patients with NP and nosocomial BSI (MM) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| *% of carbapenem-resistant clones in nosocomial bacterial infections* | *4.0%* | *4.0%* | *4.1%* | *4.1%* | *4.2%* | *4.2%* | *4.2%* | *4.3%* |
| Annual number of carbapenem resistant NP and nosocomial BSI cases | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Annual number of CRE cases (MM) | 0.08 | 0.08 | 0.08 | 0.09 | 0.09 | 0.09 | 0.09 | 0.09 |
| *% of patients treated with plazomicin* | 2.0% | 8.0% | 14.0% | 18.0% | 20.0% | 22.0% | 24.0% | 25.0% |
| Number of patients treated with plazomicin (MM) | 0.002 | 0.007 | 0.012 | 0.015 | 0.017 | 0.020 | 0.022 | 0.023 |
| Cost per treatment cycle | $1,875 | $15,000 | $15,450 | $15,914 | $16,391 | $16,883 | $17,389 | $17,911 |
| **U.S. Total Plazomicin Revenue ($MM)** | **$3.0** | **$98.7** | **$181.5** | **$245.2** | **$286.3** | **$330.8** | **$379.2** | **$415.1** |
| **ROW** | | | | | | | | |
| Annual number of CRE cases (MM) | | 0.10 | 0.10 | 0.10 | 0.10 | 0.11 | 0.11 | 0.11 |
| *% of patients treated with plazomicin* | | 5.0% | 9.0% | 12.0% | 14.0% | 16.0% | 18.0% | 20.0% |
| Number of patients treated with plazomicin (MM) | | 0.005 | 0.009 | 0.012 | 0.015 | 0.017 | 0.020 | 0.022 |
| Cost per treatment cycle | | $10,500 | $10,815 | $11,139 | $11,474 | $11,818 | $12,172 | $12,538 |
| ROW Total Plazomicin Revenue ($MM) | | 51.8 | 98.0 | 137.3 | 168.3 | 202.1 | 238.9 | 278.9 |
| **ROW Royalty Revenue Booked by Achaogen ($MM) (15% - 25%)** | | **$7.8** | **$17.6** | **$24.7** | **$30.3** | **$40.4** | **$47.8** | **$55.8** |
| **WW Total Sales and Royalty Revenue Booked by Achaogen ($MM)** | **$3.0** | **$106.5** | **$199.1** | **$269.9** | **$316.6** | **$371.3** | **$427.0** | **$470.8** |

Source: Cowen and Company

## Achaogen, Inc. Quarterly P&L Model ($MM)

| | 2012A | Q1-Q3:13A | Q4:13A | 2013A | Q1:14E | Q2:14E | Q3:14E | Q4:14E | 2014E |
|---|---|---|---|---|---|---|---|---|---|
| Plazomicin Sales Revenue | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Plazomicin Royalty Revenue | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Contract Revenue | 17.9 | 12.3 | 6.2 | 18.5 | 6.3 | 6.5 | 6.6 | 6.6 | 26.0 |
| **Total Revenues** | **17.9** | **$12.3** | **$6.2** | **$18.5** | **$6.3** | **$6.5** | **$6.6** | **$6.6** | **$26.0** |
| COGS | - | - | - | - | - | - | - | - | - |
| Research and Development | 26.6 | 16.7 | 6.8 | 23.5 | 6.9 | 8.8 | 9.4 | 9.9 | 35.0 |
| General and Administrative | 7.3 | 5.4 | 1.6 | 7.0 | 1.6 | 1.7 | 1.8 | 1.9 | 7.0 |
| Sales | - | - | - | - | - | - | - | - | - |
| **Total Operating Expenses** | **33.9** | **22.1** | **8.4** | **30.5** | **8.5** | **10.5** | **11.2** | **11.8** | **42.0** |
| **Income (Loss) from Operations** | **($16.0)** | **($9.8)** | **($2.2)** | **($12.0)** | **($2.2)** | **($4.0)** | **($4.6)** | **($5.2)** | **($16.0)** |
| Interest Expense and Other, net | (2.4) | (1.1) | (0.2) | (1.3) | (1.3) | (1.3) | (1.3) | (1.3) | (5.3) |
| Interest Income and Other, net | 0.1 | 0.3 | (0.1) | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Net Income (Loss)** | **($18.4)** | **($10.6)** | **($2.5)** | **($13.1)** | **($3.5)** | **($5.3)** | **($5.9)** | **($6.5)** | **($21.3)** |
| *Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* |
| Income Tax | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Net Income (Loss) Attributable to Common Shareholders** | **(18.4)** | **(10.6)** | **(2.5)** | **(13.1)** | **(3.5)** | **(5.3)** | **(5.9)** | **(6.5)** | **(21.3)** |
| **GAAP EPS, Basic and Diluted** | **($4.80)** | **($2.50)** | **($0.58)** | **($3.08)** | **($0.80)** | **($0.29)** | **($0.32)** | **($0.34)** | **($1.40)** |
| Weighted Average Shares Outstanding - Basic and Diluted | 3.8 | 4.2 | 4.3 | 4.3 | 4.4 | 18.6 | 18.8 | 19.0 | 15.2 |

Source: Cowen and Company

## Achaogen, Inc. Annual P&L Model ($MM)

| | 2012A | 2013A | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Plazomicin Sales Revenue | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 3.0 | 98.7 | 181.5 | 245.2 | 286.3 |
| Plazomicin Royalty Revenue | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 7.8 | 17.6 | 24.7 | 30.3 |
| Contract Revenue | 17.9 | 18.5 | 26.0 | 28.0 | 23.0 | 17.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Total Revenues** | **17.9** | **$18.5** | **$26.0** | **$28.0** | **$23.0** | **$17.5** | **$3.0** | **$106.5** | **$199.1** | **$269.9** | **$316.6** |
| COGS | - | - | - | - | - | - | 0.5 | 13.8 | 23.6 | 29.4 | 31.5 |
| Research and Development | 26.6 | 23.5 | 35.0 | 34.0 | 34.5 | 30.0 | 28.0 | 28.0 | 28.0 | 30.0 | 32.0 |
| General and Administrative | 7.3 | 7.0 | 7.0 | 7.5 | 8.0 | 8.5 | 9.5 | 11.0 | 12.5 | 14.0 | 15.0 |
| Sales | - | - | - | - | - | - | 4.5 | 8.0 | 8.4 | 8.8 | 9.3 |
| **Total Operating Expenses** | **33.9** | **30.5** | **42.0** | **41.5** | **42.5** | **38.5** | **42.5** | **60.8** | **72.5** | **82.2** | **87.7** |
| **Income (Loss) from Operations** | **($16.0)** | **($12.0)** | **($16.0)** | **($13.5)** | **($19.5)** | **($21.0)** | **($39.4)** | **$45.7** | **$126.7** | **$187.7** | **$228.8** |
| Interest Expense and Other, net | (2.4) | (1.3) | (5.3) | (1.3) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Interest Income and Other, net | 0.1 | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Net Income (Loss)** | **($18.4)** | **($13.1)** | **($21.3)** | **($14.8)** | **($19.5)** | **($21.0)** | **($39.4)** | **$45.7** | **$126.7** | **$187.7** | **$228.8** |
| *Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *8%* | *13%* | *18%* |
| Income Tax | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 10.1 | 24.4 | 41.2 |
| **Net Income (Loss) Attributable to Common Shareholders** | **(18.4)** | **(13.1)** | **(21.3)** | **(14.8)** | **(19.5)** | **(21.0)** | **(39.4)** | **45.7** | **116.5** | **163.3** | **187.6** |
| **GAAP EPS, Basic and Diluted** | **($4.80)** | **($3.08)** | **($1.40)** | **($0.76)** | **($0.93)** | **($0.78)** | **($1.38)** | **$1.52** | **$3.24** | **$4.41** | **$4.94** |
| Weighted Average Shares Outstanding - Basic and Diluted | 3.8 | 4.3 | 15.2 | 19.5 | 21.0 | 27.0 | 28.5 | 30.0 | 36.0 | 37.0 | 38.0 |

Source: Cowen and Company

# *Valuation Methodology And Risks*

## Valuation Methodology

**Biotechnology:**
In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

## Investment Risks

**Biotechnology:**
There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

## Risks To The Price Target

Our price target is based on our projection that the ongoing pivotal Phase III clinical trial of plazomicin will generate positive data to support both FDA and EMA approvals. However, although Achaogen has completed a Phase II clinical trial in cUTI and data from both *in vitro* and preclinical studies suggest strong activity of plazomicin for CRE infections, there is no guarantee that the Phase III clinical trial will be successful. Moreover, any failure in management's execution will affect the product launches and market uptake even after FDA approvals. We believe plazomicin is highly differentiated from currently available antibiotics and other drug candidates in clinical development for Gram-negative pathogens. However, any new products entering the market may potentially change the competition dynamics and can negatively impact the market shares that plazomicin can garner.

# Addendum

## Stocks Mentioned In Important Disclosures

| Ticker | Company Name |
|---|---|
| ACAD | Acadia Pharmaceuticals |
| AKAO | Achaogen |
| CEMP | Cempra |
| HZNP | Horizon Pharma |
| ITCI | Intra-Cellular Therapies |

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**COWEN AND COMPANY RATING DEFINITIONS**

***Cowen and Company Rating System effective May 25, 2013***

**Outperform (1):** The stock is expected to achieve a total positive return of at least 15% over the next 12 months

**Market Perform (2):** The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

**Underperform (3):** Stock is expected to achieve a total negative return of at least 10% over the next 12 months

**Assumption:** The expected total return calculation includes anticipated dividend yield

***Cowen and Company Rating System until May 25, 2013***

**Outperform (1):** Stock expected to outperform the S&P 500

**Neutral (2):** Stock expected to perform in line with the S&P 500

**Underperform (3):** Stock expected to underperform the S&P 500

**Assumptions:** Time horizon is 12 months; S&P 500 is flat over forecast period

***Cowen Securities, formerly known as Dahlman Rose & Company, Rating System until May 25, 2013***

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**Hold** – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

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| Rating | Count | Ratings Distribution | Count | IB Services/Past 12 Months |
|---|---|---|---|---|
| Buy (a) | 407 | 57.08% | 85 | 20.88% |
| Hold (b) | 288 | 40.39% | 8 | 2.78% |
| Sell (c) | 18 | 2.52% | 1 | 5.56% |

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's ratings definitions.

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**Acadia Pharmaceuticals Rating History as of 04/04/2014**

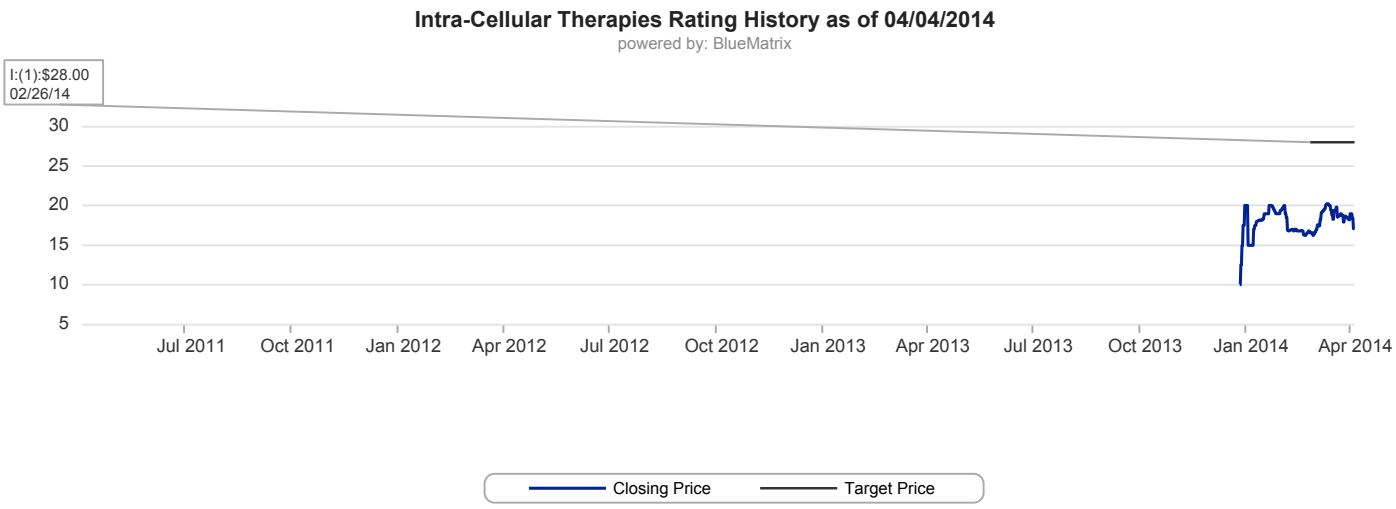
powered by: BlueMatrix


**Cempra Rating History as of 04/04/2014**

powered by: BlueMatrix


**Horizon Pharma Rating History as of 04/04/2014**

powered by: BlueMatrix




**Legend for Price Chart:**

I = Initation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | $xx = Price Target | NA = Not Available

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