



**Company Report: Paratek Pharmaceuticals;  
PRTK**

**March 28, 2017**



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## AMP Biotech Research

### **Company:** Paratek; NASDAQ: PRTK

#### Financials

Market Cap: \$427M

Cash: ~\$128M (as of 4Q16)

Debt: \$39M (as of 4Q16)

Burn: \$26M/Q (as of 4Q16)

#### **Near-term Binary Events:**

- Phase 3 data of oral only omadacycline in patients with acute bacterial skin and skin structure infections (ABSSSI) due 2Q17
- Phase 3 data of IV/oral omadacycline in patients with community-acquired bacterial pneumonia due 2Q17

*Investment Thesis:* Paratek's new class of antibiotics offers a broad-spectrum alternative to treat resistant infections. We see the market giving a high probability of success for omadacycline in skin infections and therefore value is mostly accounted for in the price. However, we see unrealized value in community-acquired bacterial pneumonia and complicated urinary tract infection. Furthermore, the potential of sarecycline outside the U.S. offers an additional opportunity at upside should a partnership deal get executed.

**Background and context:** Paratek Pharmaceuticals is a clinical stage company with a focus in next-generation tetracycline-derived antibiotics. Paratek has prestigious roots and was founded by Nobel prize-winning chemist and Founder of Biogen, Dr. Wally Gilbert and Dr. Stuart Levy, the Director of the Center for Adaptation Genetics and Drug Resistance and Distinguished Professor at Tufts University. Paratek was founded to address the growing need for alternative antibiotics as mechanisms for resistance continue to grow.

Their lead asset, omadacycline, falls within a new class of antibiotics called aminomethylcyclines. These antibiotics are derivatives of tetracycline that have been specifically designed to overcome the two major mechanisms of tetracycline resistance, drug efflux and ribosomal protection. Like their tetracycline ancestor, these antibiotics also display broad-spectrum activity affecting gram positive, gram negative, and atypical bacteria. Omadacycline has Qualified Infectious Disease Product (QIDP) designation and Fast Track status with the FDA. Pending successful results with their upcoming phase 3 trials, Paratek is on track to file NDAs for skin and pneumonia indications within the first half of 2018.

Their second lead asset, sarecycline is another tetracycline derivative, but with narrow spectrum activity. It is being evaluated for the treatment of acne and recently met the primary endpoint in two Ph3 trials. U.S. rights to this asset are exclusively licensed to Allergan in exchange for milestone payments (\$17M remaining) and tiered royalties in the mid-single digits to low double digits range. In this agreement, commercialization rights outside the U.S. are retained, and it appears that Paratek



intends to out-license commercialization rights outside the U.S. as well. The next milestone is a \$5M payment upon FDA acceptance of the New Drug Application, which Allergan expects to file later this year.

#### Additional collaborations:

In October of 2016, Paratek announced a Cooperative Research and Development Agreement (CRADA) with the U.S. Medical Research Institute of Infectious Disease to study whether omadacycline can be used to combat specific pathogens that pose a threat to public health. These include potential bio-terrorism agents such as *Yersinia pestis*, the causative agent of plague and *Bacillus anthracis*, the bacterium that produces the anthrax toxin. The first findings from this collaboration were published in February 2017 and demonstrated that omadacycline was active against both agents, with decreased potency against *Y. pestis* and increased potency against *B. anthracis* when compared to ciprofloxacin. In general, we see this agreement as a positive sign for the future development of omadacycline as it could result in an additional use for the antibiotic and could increase the overall manufacturing demand to generate precautionary stockpiles. Furthermore, in the near-term, it has the potential to unlock sources of non-dilutive capital from the military budget.

#### Preclinical data

The preclinical work on omadacycline is extensive. For brevity, here we will only briefly discuss the spectrum of antibacterial activity of omadacycline. Omadacycline has demonstrated activity *in vitro* against a wide array of bacteria including gram-positive aerobes, resistance gram-positive pathogens including methicillin-resistance *S. aureus* (MRSA), multi-drug resistant *S. pneumoniae*, and vancomycin-resistance enterococci (VRE), plus many gram-negative aerobes, and some anaerobes and atypical bacteria.

#### Clinical data

Paratek has completed three double blind, placebo-controlled multi-center studies evaluating omadacycline in patients with skin infection. This includes one Ph2b and two Ph3 studies. All three studies demonstrated clinical efficacy, although the first Ph3 trial was cut short as the FDA wanted to change the primary endpoint. In the most recent trial (June 2016), Paratek announced positive phase 3 data of IV to oral omadacycline in patients with acute bacterial skin and skin structure infections (ABSSSI). In this trial, omadacycline was evaluated for non-inferiority to twice daily linezolid. The primary endpoint was an Early Clinical Response (ECR) defined as a reduction in lesion size greater than 20%, 48-72 hours after the first dose. The ECR for omadacycline was 84.8% vs 85.5% with linezolid. Clinical success rates were 86.1% with omadacycline vs 83.6% with linezolid. Adverse events were similar between groups with GI events being most common. To satisfy EMA (European Medicines Agency) requirements, additional co-primary endpoints included the investigators assessment of clinical response at the post treatment evaluation (PTE) in the modified Intent to Treat (mITT) and clinically evaluable (CE) populations. Omadacycline met the primary endpoint of non-inferiority (10% margin) for both of these populations when compared with linezolid. At the PTE, clinical success rates in the mITT were 86.1% and 83.6% for omadacycline and linezolid, respectively. In the CE population at PTE, omadacycline had a 96.3% clinical success rate compared with 93.5% for linezolid. Overall, clinical efficacy with omadacycline was comparable to that achieved by linezolid.

#### Near-term Binary Events

##### ABSSSI

Given the ABSSSI data presented in June, and the totality of the data available, we believe there is a high likelihood of success in the oral-only Ph3 trial. For this same reason, positive data is unlikely to impact price significantly. This Ph3 study is designed very



similarly to the previous oral/IV ABSSSI study with the primary endpoint and the EMA co-primary endpoints being identical.

## **CABP**

In the community-acquired bacterial pneumonia (CABP) study, the primary efficacy endpoint for the FDA is the number of subjects with clinical success at the ECR assessment visit, which is set to occur 72-120 hours after the first dose. The EMA co-primary endpoints are the Investigator's Assessment of Clinical Response 5-10 days after the completion of treatment for the ITT and CE populations. Additional efficacy outcome measures include overall survival and improvement of signs and symptoms at the post treatment evaluation. Safety and tolerability will be assessed via treatment-emergent adverse events, laboratory values, and vital sign measurements. This study will enroll ~750 patients and as aforementioned, has been designed to satisfy both FDA and EMA requirements.

While it is unwise to interpret success in ABSSSI as an indicator that this trial will also be successful, we believe there are several reasons to expect a positive outcome. According to etiological evaluations of CABP, the majority of cases result from infection with *S. pneumoniae*. From preclinical work, it has been established that omadacycline exhibits potent activity against this pathogen *in vitro* with a minimum inhibitory concentration (MIC)<sub>90</sub> of 0.06 µg/mL and *in vivo* with an overall bactericidal activity against several strains with prior phenotypic resistance to antibacterials. To a lesser extent, other potential causes of CABP include lung infection with *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *H. influenzae*, *Legionella spp.* and atypical or mixed bacterial/viral infection. Omadacycline MIC<sub>90</sub> against *M. pneumoniae*, and *H. influenzae*, was 2 µg/mL, and 1 µg/mL, respectively.

Of course, these data are from clinical isolates evaluated *in vitro* and so how this might play out in a tissue is yet to be established. However, to provide some reference for the potential concentrations of omadacycline in lung tissue, Paratek evaluated concentrations over time and found that omadacycline concentrations in lung alveolar cells exceeded 10 µg/mL over a 24-hour period. They also found that levels in plasma and the lung lining fluid exceeded 1 µg/mL after 1 hour and ended at 0.4 µg/mL at 24 hours. These data, while correlative, suggest omadacycline should achieve meaningful levels at the site of infection. Given that the majority of CABP is caused by *S. pneumoniae*, we believe omadacycline has a good chance of meeting the non-inferiority endpoint of this Ph3 trial set to read out in 2Q17. In our view, this trial represents a significant value-inflection point and could result in a substantial move in price.

## **Additional notes on clinical trial design and execution:**

Management has indicated that they spend considerable time and effort to ensure that clinical trial sites are up to date with best clinical practices. This is an important consideration, especially for trials evaluating infectious diseases that can become compromised with the emergence of bacterial resistance and nosocomial infections.

## **Markets**

From Paratek's estimates, the total addressable U.S. hospital market is valued just shy of a \$4B opportunity. They estimate the total addressable U.S. community market is over \$5B. This assumes success in the three major indications including skin, lung, and UTI. While these estimates initially seem high for a second-line treatment, this market is validated by sales data from comparable broad-spectrum antibiotics with a similar product profile. Even if omadacycline only penetrates 10% of this addressable market, that would put peak sales over \$900M. With a current market capitalization of \$400M, this represents significant upside.

## Competition

Competition in the antibiotics space is steep. However, companies developing new agents have steadily decreased every year since the early 1980s leaving a near-term void as resistance develops against old generics. Furthermore, over the last 15 years, the majority of approved antibiotics have been targeted agents with IV-only formulations. Of the companies that are working to fill this unmet need, Cempra and Achaogen are the two closest competitors. Cempra's lead candidate solithromycin recently received a Complete Response Letter (CRL) from the FDA referencing potential hepatic toxicity issues. In contrast, safety of omadacycline has been extensively studied, including in patients with mild, moderate, and severe hepatic impairment. The findings from these studies demonstrated no effect on hepatic function with both oral and IV dosing. This coupled with solithromycin recently failing to meet the non-inferiority endpoint for their study in gonorrhea patients suggests its clinical uptake will be modest at best. Achaogen's lead candidate is an aminoglycoside designed to overcome resistance mechanisms. While it has seen success in the clinic in patients with complicated UTI, it is only effective against gram-negative bacteria, limiting its total addressable market.

Finally, omadacycline has demonstrated a further competitive edge in the area of *C. difficile* infection (CDI) secondary to IV antibiotics. In preclinical work, while omadacycline did disrupt the intestinal microbiota, it did not result in *C. difficile* infection (CDI) as measured by toxin production, vegetative cell proliferation or *C. difficile* germination. This finding corroborates previous work with tetracyclines that demonstrated that these antibiotics actually decreased risk of CDI, in contrast to many antibiotics that increased risk. The CDC has reported that if hospitals reduce the use of drugs known to provoke CDI by 30%, there would be a predicted 26% reduction in CDI. These findings differentiate omadacycline from other antibiotics and could provide a significant competitive advantage over alternative antibiotics in development and on the market.

## Summary

Paratek pharmaceuticals is well positioned to provide an additional broad-spectrum antibiotic for the 3 major infectious disease markets. Omadacycline's unique product profile provides features that will enable it to compete in a competitive market. With the total value of this asset yet to be realized, we see significant upside potential as it gains additional clinical evidence of efficacy and safety.

For more information see: <http://paratekpharma.com/about/>

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