# Durata Therapeutics, Inc. (DRTX)

Initiating Coverage of Durata Therapeutics with Market Outperform Rating and $12 Price Target

**MARKET DATA**

| | |
|---|---|
| Price | $6.85 |
| 52-Week Range: | $6.65 - $10.63 |
| Shares Out. (M): | 26.6 |
| Market Cap ($M): | $182.2 |
| Average Daily Vol. (000): | 101.0 |
| Cash (M): | $100 |
| LT Debt (M): | $0 |

Source: Thomson Reuters and JMP Securities LLC

| FY DEC | | 2012A | 2013E | 2014E |
|---|---|---|---|---|
| Revenue ($M) | 1Q | $0.0 | $0.0A | -- |
| | 2Q | $0.0 | $0.0 | -- |
| | 3Q | $0.0 | $0.0 | -- |
| | 4Q | $0.0 | $0.0 | -- |
| | **FY** | **$0.0** | **$0.0** | **$16.4** |
| EPS | 1Q | ($142.69) | ($0.86)A | -- |
| | 2Q | ($260.25) | ($0.54) | -- |
| | 3Q | ($1.47) | ($0.55) | -- |
| | 4Q | ($0.72) | ($0.55) | -- |
| | **FY** | **($7.48)** | **($2.49)** | **($1.96)** |
| | P/E | NM | NM | NM |

Source: Company reports and JMP Securities LLC

**STOCK PRICE PERFORMANCE**


**MARKET OUTPERFORM** | Price: $6.85 | Target Price: $12.00

## INVESTMENT HIGHLIGHTS

**Initiating coverage of Durata Therapeutics with a Market Outperform rating and a $12 price target based on our risk-adjusted, discounted cash flow analysis.** Durata is preparing to file for U.S. and European approval of dalbavancin, a long-acting antibiotic delivered in two 30-minute IV infusions one week apart, for the treatment of serious skin infections. Top-line data from two Phase 3 studies show that dalbavancin successfully met the non-inferiority benchmark using proposed FDA endpoints. We believe dalbavancin could be a game changer for the treatment of MRSA infections, allowing more patients to be treated on an outpatient basis thereby affording significant cost savings. The greatest risks to our thesis include unanticipated regulatory risks and the readiness of hospitals to adopt. We are encouraged that relatively low penetration is needed to drive significant value given the size of the market where 1% share delivers roughly $100 million in revenue. Our $12 price target is based on a risk-adjusted, discounted cash flow analysis assuming a 60% chance of dalbavancin approval and $423M in revenue in 2020. We recommend owning shares of Durata now, ahead of anticipated data presentations, as well as regulatory and commercial catalysts in the coming year.

**Efficacy in five Phase 3 studies mitigates regulatory risk**. Dalbavancin has a long regulatory history, ultimately delayed due to changes in the regulatory requirements for skin infections. In support of approval, Durata ran two Phase 3 trials, DISCOVER-1 and -2, following draft FDA guidelines demonstrating equal activity to the current standard of care. Although the levels of methicillin resistant staph aureus (MRSA) in the DISCOVER studies were low, we believe these limited data are supported by the previous studies where the percentage of MRSA was higher.

**Large safety database supports clean profile**. Overall, >2,000 patients have been exposed to dalbavancin in pivotal studies forming the basis of a large safety database. We believe regulatory reviews of dalbavancin will focus on safety due to the long half-life of the drug, though our review of available data suggest the safety profile of dalbavancin is undifferentiated from comparators. The recent long-term dosing study of up to eight weeks of therapy gives us confidence that the drug is not accumulating over time and may support longer-term usage.

**New paradigm in IV antibiotics**. The MRSA space is becoming increasingly crowded and will likely become more complex with forthcoming additional generic competition. Dalbavancin is differentiated by its unique dosing scheme which seems to resonate with ER physicians seeking to lower admissions and to facilitate more rapid discharge, goals that we believe will become more pronounced with the implementation of the Affordable Care Act. In our view, dalbavancin fits in well with outpatient therapy and, in our view, supports a strong pharmacoeconomic argument for usage, despite premium pricing.

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## INVESTMENT THESIS

### Large clinical database mitigates regulatory risk

Our review of the top-line data suggests dalbavancin meets the requirements for approval

Durata is preparing to file for U.S. and European approval of dalbavancin, a long-acting IV antibiotic for the treatment of serious skin infections. In the hands of Vicuron/Pfizer, dalbavancin had a turbulent relationship with regulators, ultimately failing to gain approval in both the U.S. and Europe. Since acquiring the asset in 2009, Durata augmented the data package with two Phase 3 studies in acute bacterial skin and skin structure infections (ABSSSI), DISCOVER-1 and -2, under the auspices of a special protocol assessment (SPA) and newly proposed guidelines.

Our review of the top-line data suggests that dalbavancin has met the requirements for approval. However, we point out that the full data set has not yet been presented and as such, our analysis is relatively superficial. From this vantage point, our key concern, and one that we believe could be a wildcard for an FDA advisory meeting, is low representation of MRSA in the latest Phase 3 program. However, we point out that the prior sponsors completed a study specifically addressing MRSA without an issue, and management does not believe that MRSA is a regulatory risk.

In our view, dalbavancin's long half-life could also be a source of additional regulatory scrutiny over the potential for resistance and safety issues. Nothing notable stands out in our review of the available safety data. Furthermore, in earlier reviews, safety was not flagged and since then the evidence for safety has only improved with additional studies, including the two Phase 3 studies, a long-term dosing study demonstrating no drug accumulation, a QTc study, and a study with patients with impaired renal function.

### Differentiated from the pack

Dalbavancin is administered by two 30-minute intravenous (IV) infusions separated by one week, which makes it ideal for outpatient administration

After a 10+ year hiatus, regulatory clarity has breathed life into the antibiotic field, and we foresee a slew of new drug launches beginning in 2014. Dalbavancin is administered by two 30-minute intravenous (IV) infusions separated by one week. This approach is unique amongst the current and future competition which require daily dosing, namely vancomycin, linezolid, daptomycin, and potentially tedizolid. Oritavancin, a Phase 3 antibiotic, is dosed just once, but requires a 3-hour infusion, which could be an issue for the emergency room setting, if approved.

There are meaningful economic implications to once-weekly dosing, most of which stem from the compatibility with outpatient administration. A physician survey conducted by Durata suggests that, on average, about 25% of hospital admissions for gram positive infections could be avoided by a more convenient treatment option. Moreover, emergency room physicians we have spoken with are excited to use dalbavancin, believing it can provide a compelling alterative to vancomycin in the ER setting, comparing it to the same treatment a patient would get 'in hospital'. With the backdrop of the Affordable Care Act, as well as a continued push toward profitability in the hospital setting, we believe the timing for dalbavancin could be right. That being said, there is a spectrum of readiness for dalbavancin amongst hospitals, the distribution of which, in our opinion, is the biggest commercial risk.

We believe dalbavancin is well suited for infections requiring long-term therapy

### Skin infections a gateway to other indications

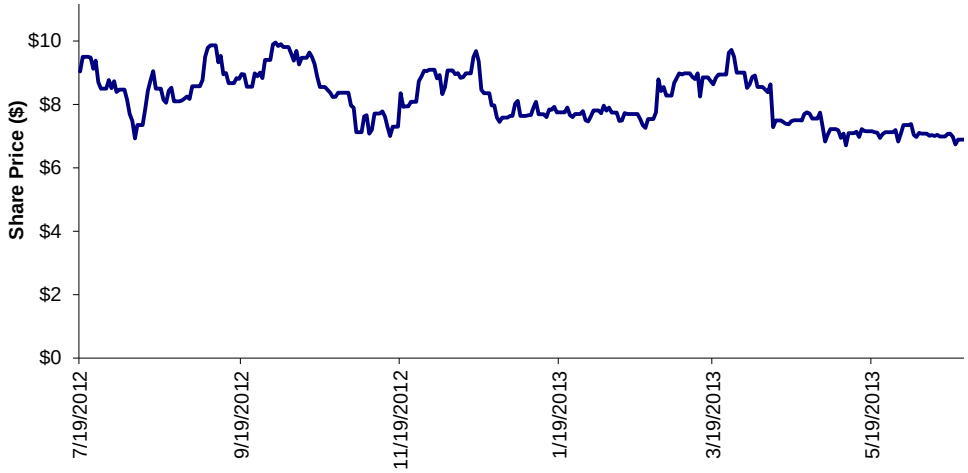
As is the case for other antibiotics, if approved for ABSSSI, we anticipate a fair degree of off-label usage. We believe dalbavancin is well suited for infections requiring long-term therapy including osteomyelitis and diabetic foot infection. As part of its lifecycle management plan, Durata has a series of initiatives forthcoming toward facilitating off-label usage, though the company may not officially seek approval given regulatory barriers. Management has also indicated an interest in pursuing pneumonia as a labeled indication.

### Compelling valuation

Shares of Durata have not participated in the recent surge in biotech valuation. We believe the root cause of this relatively poor performance is the perceived risk of forthcoming catalysts, which are primarily regulatory and commercial in nature. Recent history has not been kind to some antibiotics in this regard. Moreover, we anticipate increased generic competition beginning in 2015. The FDA has since clarified its requirements for approval and we believe dalbavancin has met the specified hurdle.

Commercially, we think dalbavancin has the potential to be a game changer for the MRSA market. In our opinion, the success of daptomycin in the outpatient setting makes the case for the potential success of dalbavancin. Further, we point out that only a small share of the market is necessary to drive significant revenue acceleration. Our sensitivity analysis shows that 1% share of the MRSA market translates to about $100 million in revenue, assuming prices comparable to current premium priced antibiotics. We currently model 4% share of the gram (+) market, or $423 million net revenue at peak in 2020, risk adjusted to reflect a 60% chance of reaching the market which drives our $12 price target, almost 80% above current levels. We believe the stock should appreciate with the presentation of the Phase 3 data set in the upcoming fall medical meeting cycle, but may be volatile during the regulatory review process and should appreciate with a successful launch.

**FIGURE 1. DRTX Price Chart**




*Source: Thompson Reuters and JMP Securities LLC*

## VALUATION

Our $12 price target is based on a risk-adjusted, discounted cash flow analysis (DCF) using a discount rate of 9% derived from CAPM

The value of Durata, in our view, is derived solely from dalbavancin, a novel gram (+) antibiotic which, if approved, will be used to treat patients suspected of harboring serious MRSA infections. Our $12 price target is based on a 40% risk-adjusted, discounted cash flow analysis (DCF) using a discount rate of 9% derived from a CAPM analysis and a 0% assumption for terminal growth given our belief that dalbavancin will face its own generic competition beginning in 2027 (Figure 5). Our implied valuation of $370 million compares favorably to other antibiotic companies (Figure 2).

Below we describe the key assumptions used in our model.

**FIGURE 2. Comparable Company Analysis**

| Company | 6/24/2013 Stock Price | Market Cap ($mil.) | Cash ($mil.) | Debt ($mil.) | EV ($mil) | Lead Product | Indication | Stage of Dev. |
|---|---|---|---|---|---|---|---|---|
| Optimer | $13.57 | $652 | $93 | $0 | $558.3 | Dificid | CDI | Marketed |
| Trius | $7.98 | $382 | $84 | $0 | $298.3 | Tedizolid | MRSA | Phase 3 |
| Cubist | $49.31 | $3,213 | $853 | $371 | $2,732.1 | Cubicin | MRSA | Marketed |
| Tetraphase | $7.80 | $133 | $77 | $88 | $143.3 | Eravacycline | Gram (-) | Phase 2 |
| | | | | **Mean** | **$933.03** | | | |
| Durata | $6.85 | $182 | $100* | $18.4 | $100.62 | Dalbavancin | MRSA | Phase 3 |

** pro forma*

*Source: Company reports and JMP Securities LLC*

Durata is currently preparing to submit dossiers for approval of dalbavancin in the U.S. and Europe. To augment the data set generated by prior sponsors, Durata completed two Phase 3 studies in ABSSSI, which will be the basis for approval. While the full data set has not yet been officially presented, our analysis of the top-line data suggests they have met the required endpoints for approval, as outlined in the SPA. Our key critique of the data is the low representation of confirmed MRSA infections, which we identify as the primary clinical data risk to approval. Ahead of reviewing the Phase 3 data and the FDA's assessment of the data package, we assign a 60% chance of approval. Therefore, we discount our revenue projections by 40%.

While the incidence of MRSA in the U.S. is relatively flat, it continues to represent the most common infection type presenting to hospital emergency units. There are 35 million days of therapy for gram (+) MRSA bacterial infections in the U.S. with about 85% of those days of therapy in the hospital or in an outpatient setting. Current trends indicate a 2-4% growth rate in the volume of prescriptions for MRSA antibiotics, so we conservatively assume the market grows at 2% for the next seven years.

We currently assume a price of $3,900 per course of therapy, which is comparable to a 14-day course of daptomycin, but more than linezolid at $2,200 and vancomycin at about $150 per course of therapy. We think this is reasonable given the cost savings in avoiding daily IV administration that can be captured with the use of dalbavancin. Moreover, emergency room physicians we spoke with describe some latitude in prescribing expensive medications – indicating a potentially less price sensitive market.

Dalbavancin is administered as two IV doses: 1000mg/kg followed eight days later by 500mg/kg. For modeling purposes, we assign a gross price of $2,600 to the first dose and $1,300 for the second dose and a 15% gross to net adjustment to account for various payor discounts and rebates. In addition, we estimate that about 50% of patients receiving a two-week course of therapy return for the second dose whereas with treatment in indications like osteomyelitis, we assume six doses.

As a once-weekly IV antibiotic, we think dalbavancin will find the most usage in situations where patients could be treated on an outpatient basis, if not for the requirement for once- or multiple-daily IV infusions of currently available antibiotics, or where there are concerns about compliance. While oral options are available for outpatient therapy, they are not always optimal - often severe infections necessitate IV therapy and oral antibiotics are associated with poor compliance. Daptomycin, a once-daily IV antibiotic marketed by Cubist, has gained significant traction in the outpatient antimicrobial market (OPAT) which, in our view, supports our thesis that dalbavancin should gain traction in this setting. Emergency room physicians we have spoken with believe dalbavancin will be viewed as a 'long-term vancomycin' providing the same level of drug therapy as if a patient were admitted to the hospital without the cost and hassle of a pic line. We believe sophisticated hospitals will recognize the potential cost savings afforded by the use of dalbavancin.

That being said, we think the competitive and reimbursement hurdles in this market are significant.

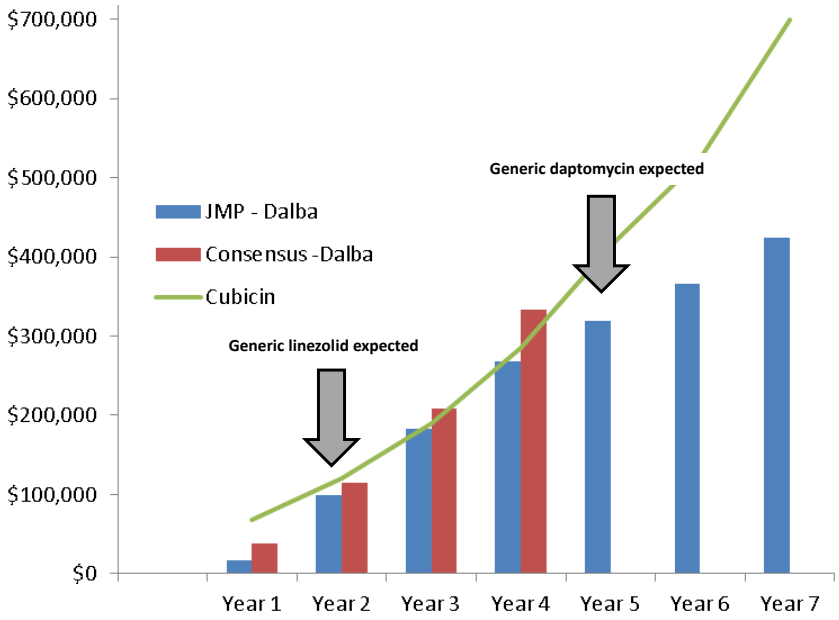
- **Competition**. Early in launch, dalbavancin will be faced with generic competition from linezolid, a once-daily IV and oral MRSA antibiotic marketed as Zyvox by Pfizer. Longer term, dalbavancin will face generic competition from daptomycin. Both these antibiotics have been commercial successes reaching $809M and $695M in the U.S. alone last year, despite premium pricing over generic vancomycin. Once generics are available, we anticipate a surge in usage of these antibiotics. In terms of convenience plays, we foresee only one potential competitor: The Medicines Company's oritavancin, a one-dose IV antibiotic with similar efficacy to dalbavancin currently in late stage development. However, this compound is associated with safety concerns regarding drug accumulation, which we believe is both a regulatory and commercial risk. In addition, we anticipate the entrance of several other newly branded competitors, including Trius' IV and oral MRSA antibiotic, tedizolid.

- **Reimbursement.** Given the pricing pressure from hospitals and our anticipation of an increase in generic competition, we believe dalbavancin will likely gain the most traction in the outpatient setting – specifically emergency department observation units (EDOU) and OPAT – where hospitals will not have to absorb the cost of drug therapy. About 25% of the targeted 1,900 hospitals have EDOUs, and dalbavancin could have appeal as hospitals continue to seek ways to avoid admission and shift the cost to a drug benefit rather than bundled in the hospital payment. OPAT is another ideal setting for dalbavancin given lower nursing costs needed for IV infusions, however, we point out that Medicare does not provide reimbursement for in-home delivery of IV antibiotics, which will limit its utility in this setting.

Considering these factors, we model a launch trajectory that tracks with early daptomycin sales (Figure 3), which we believe is a reasonable proxy for dalbavancin considering the initial indication of skin infection and positioning for both in and outpatient usage against cheaper generic alternatives. Our longer term projections for dalbavancin deviate from daptomycin given daptomycin's eventual approval for bacteremia and endocarditis three years after launch, which we do not expect for dalbavancin, and increased generic competition beginning in 2015. Thus, we project U.S. peak gross demand of $510 million in 2020 in the U.S., corresponding to $408 million net revenue (Figure 6). We note that our model is extremely sensitive to penetration assumptions, where 1% penetration results in about $100 million in gross sales.

We currently assume that Durata commercializes dalbavancin in the U.S. and finds a European partner to commercialize the antibiotic there. In Europe, the MRSA market is smaller with 15 million days of therapy and lower pricing. Assuming a 20% royalty to Durata on sales, we arrive at peak royalty revenue of $15 million from Europe.

**FIGURE 3. Revenue Projections for Dalbavancin Compared to Cubicin (Historical)**




*Source: Thompson Reuters, Company reports, and JMP Securities LLC*

We believe forthcoming catalysts (Figure 4) will de-risk the stock, generating incremental value for shareholders as dalbavancin nears commercialization.

**FIGURE 4. Upcoming Catalysts**

| Timing | Event | Product | Indication |
|---|---|---|---|
| 2H13 | File NDA | Dalbavancin | ABSSSI |
| 2H13 | Presentation of Phase 3 data | Dalbavancin | ABSSSI |
| 2H13 | Acceptance of NDA filing | Dalbavancin | ABSSSI |
| 2H13 | File MAA | Dalbavancin | ABSSSI |
| 2H13 | Phase 1 brochial study | Dalbavancin | Pneumonia |
| 2H13 | Bone penetration data | Dalbavancin | Osteomyelitis |
| 1H14 | Advisory committee meeting | Dalbavancin | ABSSSI |
| 1H14 | Approval US | Dalbavancin | ABSSSI |
| 2H14/1H15 | Approval EU | Dalbavancin | ABSSSI |

*Source: Company reports and JMP Securities LLC*

## FIGURE 5. Discounted Cash Flow Analysis

| Discounted Cash Flow Valuation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | Terminal |
| **Revenues** | 0 | 16,420 | 98,959 | 182,855 | 268,054 | 318,906 | 366,454 | 423,640 | |
| COGS | - | 821 | 9,896 | 18,234 | 26,548 | 31,399 | 35,650 | 40,884 | |
| SG&A | 16,693 | 30,000 | 60,000 | 80,000 | 100,000 | 125,000 | 150,000 | 180,000 | |
| R&D | 40,092 | 55,000 | 75,000 | 90,000 | 75,000 | 60,000 | 50,000 | 50,000 | |
| **Operating Income (EBIT)** | **(56,785)** | **(69,401)** | **(45,937)** | **(5,379)** | **66,506** | **102,507** | **130,804** | **152,756** | |
| | | | | | | | | | |
| **Weighted Risk** | 0% | 60% | 60% | 60% | 60% | 60% | 60% | 60% | |
| *Dalbavancin-US* | 0% | 60% | 60% | 60% | 59% | 59% | 58% | 58% | |
| *Dalbavancin ex-US* | 0% | 0% | 0% | 0% | 1% | 1% | 2% | 2% | |
| Tax | 0% | 0% | 0% | 0% | 25% | 40% | 40% | 40% | |
| **Risk adjusted Net Income** | - | (41,641) | (27,562) | (3,227) | 29,928 | 36,902 | 47,089 | 54,992 | 632,851 |
| **NPV** | **$365,805** | | | | | | | | |
| + Current Cash & Equivalents | $ 3,924 | | | | | | | | |
| **Value of the Company** | **$ 369,729** | | | | | | | | |
| - L-T Debt | $ 20,000 | | | | | | | | |
| **Value of Equity** | **$ 349,729** | | | | | | | | |
| **Value per Share** | **$ 11.87** | | | | | | | | |

*Source: JMP Securities LLC and Company reports*

## FIGURE 6. JMP Securities Income Statement for Durata Therapeutics

| | 2012A | 1Q13A | 2Q13E | 3Q13E | 4Q13E | 2013E | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Product revenue | | | | | | 0 | 16,420 | 98,959 | 182,855 | 268,054 | 318,906 | 366,454 | 423,640 |
| Dalbavancin sales | | | | | | | 16,420 | 98,959 | 182,336 | 265,479 | 313,994 | 356,500 | 408,838 |
| Dalbavancin royalties | | | | | | | 0 | 0 | 519 | 2,575 | 4,912 | 9,954 | 14,802 |
| **Total revenue** | **0** | **0** | **0** | **0** | **0** | **0** | **16,420** | **98,959** | **182,855** | **268,054** | **318,906** | **366,454** | **423,640** |
| Cost of goods sold | | | | | | | 821 | 9,896 | 18,234 | 26,548 | 31,399 | 35,650 | 40,884 |
| R&D | 51,695 | 11,092 | 9,000 | 10,000 | 10,000 | 40,092 | 55,000 | 75,000 | 90,000 | 75,000 | 60,000 | 50,000 | 50,000 |
| SG&A | 9,788 | 4,050 | 4,131 | 4,214 | 4,298 | 16,693 | 30,000 | 60,000 | 80,000 | 100,000 | 125,000 | 150,000 | 180,000 |
| Acquisition related charges | 1,097 | 284 | | | | | | | | | | | |
| **Total operating expenses** | **62,580** | **15,426** | **13,131** | **14,214** | **14,298** | **57,069** | **85,821** | **144,896** | **188,234** | **201,548** | **216,399** | **235,650** | **270,884** |
| **Operating income (loss)** | **(62,580)** | **(15,426)** | **(13,131)** | **(14,214)** | **(14,298)** | **(57,069)** | **(69,401)** | **(45,937)** | **(5,379)** | **66,506** | **102,507** | **130,804** | **152,756** |
| **Total other expense, net** | **(41)** | **(93)** | **(422)** | **(414)** | **(416)** | **(1,345)** | **(4,174)** | **(3,130)** | **(1,912)** | **(922)** | **(368)** | **206** | **297** |
| **Income before taxes** | **(62,539)** | **(15,519)** | **(13,553)** | **(14,628)** | **(14,714)** | **(58,414)** | **(73,575)** | **(49,067)** | **(7,291)** | **65,585** | **102,138** | **131,010** | **153,053** |
| Preferred stock accretion | | | | | | | | | | | | | |
| (Provision) benefit for income taxes | 0 | (248) | | | | 0 | 0 | 0 | 0 | 16,396 | 40,855 | 52,404 | 61,221 |
| **Net income (loss)** | **(62,539)** | **(15,767)** | **(13,553)** | **(14,628)** | **(14,714)** | **(58,414)** | **(73,575)** | **(49,067)** | **(7,291)** | **49,188** | **61,283** | **78,606** | **91,832** |
| **EPS** | **($7.48)** | **($0.86)** | **($0.54)** | **($0.55)** | **($0.55)** | **($2.49)** | **($1.96)** | **($1.07)** | **($0.15)** | **$1.01** | **$1.23** | **$1.53** | **$1.73** |
| Shares outstanding, basic | 8,364 | 18,368 | 25,220 | 26,690 | 26,790 | 24,267 | 37,594 | 45,722 | 47,093 | 48,506 | 49,961 | 51,460 | 53,004 |

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*Source: Company reports and JMP Securities LLC*

## ANTIBIOTIC MARKET ANALYSIS

In the U.S., there are about 35 million days of therapy for gram (+) infections

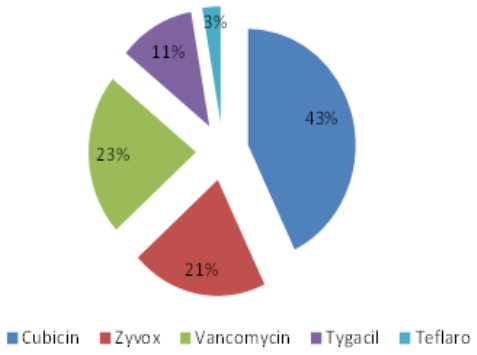
Antibiotics can be classified according to the types of pathogens they treat: gram positive (+) or negative (-), with some broad spectrum drugs treating both. In the U.S., there are about 35 million days of therapy for gram (+) infections such as skin, pneumonia, and bloodstream infections, much of which include methicillin resistant staph aureus (MRSA). U.S. rates of MRSA in skin infections have peaked at about 60%, and physicians typically treat empirically for suspicion of MRSA. This is because it takes 24-72 hours to culture and identify pathogens, which is an unacceptable delay in the initiation of therapy. Moreover, often obtaining a sample is not feasible (e.g., cellulitis). Once a physician obtains microbiological confirmation, they may or may not refine their initial decision, balancing various factors including how the infection is resolving, how the patient is tolerating the antibiotic, cost, and concerns over resistance.

U.S. rates of MRSA in skin infections have peaked at about 60%, and physicians typically treat empirically for suspicion of MRSA

Various factors play in the choice of empiric antibiotic therapy: patient history, local bacterial resistance patterns, hospital antibiotic stewardship programs instituted to control resistance, and cost.

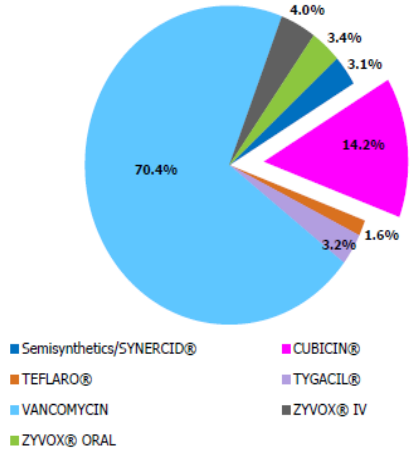
Our analysis suggests that the MRSA market is currently about $1.4B, where 23% is generic vancomycin and the remainder is branded drug sales (Figure 7). On a volume basis, generic vancomycin captures 70% share (Figure 8).

**FIGURE 7. 2012 Share by Revenue**




*Source: Company reports*

**FIGURE 8. 2012 Share by Volume**




*Source: Company reports*

In the EU, the gram (+) market is smaller with only about 10-15 million days of therapy

In the EU, the gram (+) market is smaller with only about 10-15 million days of therapy. A review of the literature suggests cases of MRSA in Europe increased from 1% in 1990 to 20% in 2007, with the rate hovering currently between 20-25%, although the real number may be higher due to inconsistent reporting.

## MARKET DYNAMICS

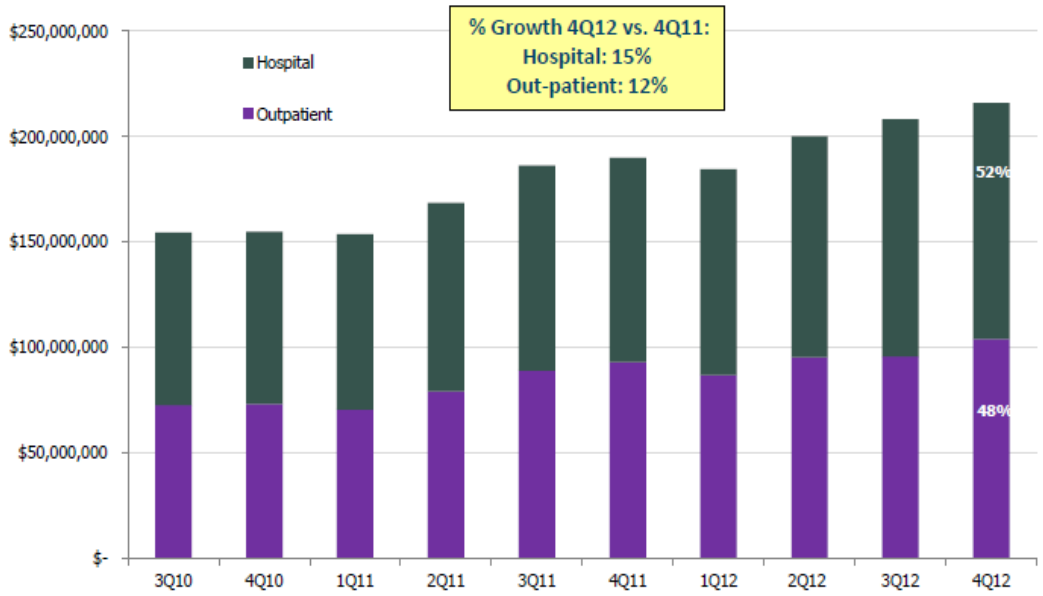
As hospitals increasingly strive to improve efficiency, reduce nosocomial infections and increase patient satisfaction, outpatient antimicrobial therapy (OPAT) has grown

### Shift to outpatient care

As hospitals increasingly strive to improve efficiency, reduce nosocomial infections and increase patient satisfaction, outpatient antimicrobial therapy (OPAT) has grown. Using Cubicin as a benchmark (Figure 9), there was about 3% growth in outpatient demand last year (net of price increases). We believe the OPAT market should experience continued growth driven by the potential launch of new antibiotics well suited for OPAT, as well as policy changes including the Affordable Care Act (ACA) which will penalize hospitals for excessive 30-day readmission rates (currently based on readmissions for heart attack, heart failure and pneumonia, but set to expand to seven indications by 2015). A factor which limits the size of this market is that Medicare does not cover OPAT antibiotic administration – a sore spot in the industry.

While vancomycin remains the most widely used antibiotic in this setting, daptomycin has made significant inroads because its once daily administration is compatible with outpatient therapy. According to Cubist, 48%, or about $400M, of daptomycin's sales were generated via OPAT at the end of 2012 (Figure 9). A review of OPAT use of daptomycin in 2005 suggests that daptomycin usage in the OPAT setting is largely driven by skin infections (both complicated and uncomplicated) with over 50% of the prescriptions, followed by about 18% for osteomyelitis, or bone infection (Figure 10).

**FIGURE 9. Cubicin Growth**




*Source: Cubist reports*

**FIGURE 10. Breakdown of Daptomycin Therapy (2005)**

| Type of infection | OPAT patients, no. (% of OPAT patients) | IPAT patients, no. (% of IPAT patients) | Total no. (% of total infections) | p-value* |
|---|---|---|---|---|
| Endocarditis | 14 (2.6%) | 15 (3.6%) | 29 (3.1%) | 0.349† |
| Bacteremia | 73 (13.5%) | 143 (34.8%) | 216 (22.8%) | < 0.001 |
| Osteomyelitis | 98 (18.2%) | 18 (4.4%) | 116 (12.2%) | < 0.001† |
| Other | 78 (14.5%) | 75 (18.3%) | 153 (16.1%) | 0.113 |
| cSSSI | 177 (32.8%) | 123 (30.0%) | 300 (31.6%) | 0.351 |
| ucSSSI | 99 (18.4%) | 36 (8.8%) | 135 (14.2%) | < 0.001 |
| Total | 539 (56.8%)‡ | 410 (43.2%)‡ | 949 (100%) | < 0.001 |

*Source: Int J Clin Pract, August 2008, 62, 8, 1183–1187*

### Observation units gaining traction

Emergency department observation units (EDOUs) are emerging as a temporary alternative to hospital admission

Emergency department observation units (EDOUs) are emerging as a temporary alternative to hospital admission. In these 'holding tanks' patients are typically observed for 4-6 hours, but up to 24-72, after which only about 20% of patients are admitted – for infections, high fever seems to be a predictor of eventual admission. According to our literature review, currently about one-third of all hospitals have observation units. Under ACA, we think EDOU's could flourish as hospitals aim to drive down admissions and readmissions.

There are important reimbursement implications for drug therapy in the EDOU, which may reduce price sensitivity. EDOUs are considered outpatient related, and so drug payments are not bundled as they are in the inpatient setting, and therefore IV infusions are considered part of the medical benefit. Therefore, the hospital does not bear the cost of IV infused medicines and hospitals may profit from using branded IV antibiotics given the ASP+6% reimbursement scheme plus the infusion fee. Cubist believes about 15% of their "in hospital" usage is actually driven by such clinics.

In 2007, about 2% or 2.5 million patients visiting the emergency room were admitted to observation. Extrapolating the growth in hospital visits from 2007 to 2010 and holding the proportion of patients admitted to observation constant suggest that in 2014, just over 3 million patients will be admitted to EDOUs. Our review of the literature suggests that cellulitis/skin infection is the reason for EDOU admission in 1-5% or an average of 93,000 patients. The portion of these cellulitis patients admitted to the hospital after an EDOU varies from institution to institution in the range of 15-38%. Interestingly, 35% of patients in the observation units are retreated with antibiotics where ~60% were treated with a MRSA antibiotic prior to admission to an EDOU which we believe indicates a compliance issue and suggests to us that a long acting IV antibiotic could find a niche in this setting as an alternative to oral therapy.

### Wave of new gram (+) antibiotics coming

After a 10+ year hiatus, regulatory clarity has breathed life into the antibiotic class, and we anticipate a slew of potential drug launches beginning in 2014

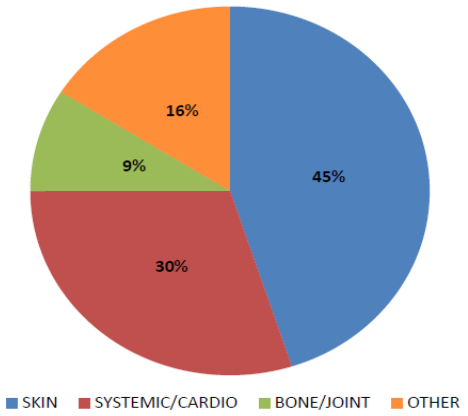
After a 10+ year hiatus, regulatory clarity has breathed life into the antibiotic class, and we anticipate a slew of potential drug launches beginning in 2014, one of which could be Durata's dalbavancin. Other molecules that could be part of the new competitive landscape include Trius's tedizolid, The Medicines Co.'s oritavancin, and generic linezolid. That being said, the gram (+) antibiotic market is large and comprised of a heterogeneous set of infections caused by different pathogens with unique susceptibilities and mechanisms of resistance and can therefore accommodate numerous products. Below we review the existing gram (+) antibiotic market with several drugs in late-stage development that could reach market in the 2014-2015 timeframe (Figure 12).

### Approved MRSA antibiotics

**Vancomycin.** Vancomycin is approved for the treatment of MRSA and endocarditis with documented effectiveness in septicemia, bone infections, lower respiratory tract infection, and skin infections. Generic vancomycin is used most often in the hospital setting, likely due to cost and activity against MRSA. That being said, resistance of MRSA to vancomycin has grown from about 3% in 2005 to 11% in 2009, reinforcing the need for new alternatives that are better tolerated and can treat resistant patients. It is a bactericidal glycopeptide and is administered 2-3 times a day by IV. Vancomycin has limitations, including side effects such as red man syndrome, an infusion reaction leading to rash, and nephrotoxicity.

**Daptomycin**. Daptomycin, marketed as Cubicin, is a novel bactericidal lipopeptide that is active against gram positive bacteria, including MRSA. It is approved for cSSSI, bacteremia, and endocarditis. Since its launch in 2003, daptomycin has captured about 13% of days of therapy for gram positive infections and is expected to eclipse $1B in revenue in 2014. We believe Cubicin has been successful, in part, because of its once daily dosing feature which facilitates its use in the outpatient setting. Daptomycin is approved for skin infections (cSSSI) and staphylococcus aureus bacteremia (SAB) including right-sided infective endocarditis (RIE) caused by MRSA and MSSA. The antibiotic does not penetrate the lung; therefore, it has not gained traction in pneumonia. In 2011, about one-quarter of use was driven by off label indications (Figure 11).

**FIGURE 11. Days of Therapy for Daptomycin by Indication (2011)**




*Source: Cubist*

## FIGURE 12. Branded MRSA Drugs on the Market or in Phase 3 Development

| | Class | Dosing | Form | Time of Injection | Cidal? | Key limitation | Indications |
|---|---|---|---|---|---|---|---|
| **Cubicin (daptomycin)** | Lipopeptide | QD | IV | 30 minutes or 2 minute push | Yes | No lung penetration | Skin, bacteremia |
| **Zyvox (linezolid)** | Oxazolidinone | BID | IV and oral | 30-120 min | No | Drug Drug interactions; myelosuppression | Skin, pneumonia, diabetic foot |
| **Tygacil (tigecycline)** | Tetracycline | BID | IV | 30-60 minutes | No | GI toxicities | Skin, intra-abdominal, pneumonia |
| **Teflaro (ceftaroline)** | Cephalosporin | BID | IV | 60 minutes | Yes | Anaphylaxis | Skin, community acq. pneumonia |
| **Vibativ (telavancin)** | Glycopeptide | QD | IV | 60 minutes | Yes | Kidney tox; prolonged QTc | Skin, nosocomial pneumonia |
| **tedizolid** | Oxazolidinone | QD | IV and oral | 60 minutes | No | n/a | Skin (NDA filing 2013); HAP/VAP trial to begin 2H13 |
| **dalbavancin** | Glycopeptide | Once a week for two weeks | IV | 30 minutes | Yes | n/a | Skin (NDA filing 2013); long term safety/bone study ongoing |
| **oritavancin** | Glycopeptide | One dose | IV | 3 hour | Yes | n/a | Skin (NDA filling 2013/2014), does not penetrate the lung |

*Source: Company reports and JMP Securities LLC*

**Linezolid.** Linezolid, marketed by Pfizer as Zyvox, is the first and only approved oxazolidinone antibiotic available as a once-daily IV or oral pill enabling 'step down' treatment strategy. Linezolid is approved for uSSSI and cSSSI, diabetic foot infections, osteomyelitis, community acquired and nosocomial pneumonia, as well as vancomycin resistant enterococci (VRE). Interestingly, it has captured less share in the U.S. than daptomycin, though global share is higher. This may be partially explained by known interactions between linezolid and monoamine oxidase (MAO) inhibitors which include the tricyclic antidepressants and some hypertensive medications. Linezolid is bacteriostatic, which limits its use in bacteremia and causes myelosuppression when the drug is dosed beyond two weeks, which limits its use in infections that require long-term dosing such as diabetic foot or osteomyelitis. The drug penetrates the lung and is therefore used in pneumonia. Linezolid requires twice a day dosing, and we believe a large part of its success is owed to its availability in either IV or oral form, where the oral form enables utilization in the outpatient setting. It is not surprising that about two-thirds of demand in the U.S. is for the tablet form and just over 40% of these prescriptions originate in the hospital. Linezolid will face generic competition in about mid-2015, which we believe will increase competition for the gram (+) market as a whole.

**Telavancin.** Telavancin, marketed as Vibativ by Theravance, is a bactericidal lipoglycopeptide in the same class as vancomycin and dalbavancin. The compound does not have strong efficacy against VanA and VanB VRE strains. Telavancin was originally approved for cSSSI and the label was recently expanded to include community and hospital pneumonia if nothing else is available. Unfortunately, it is not commercially available because of manufacturing issues. Theravance is working to establish consistent product supply that complies with regulatory requirements and may have the product available in 3Q. However, we believe the nephrotoxicity and QTc prolongation associated with the drug may limit use once drug supply is available.

### Broad spectrum antibiotics used for MRSA

**Tigecycline**. Tigecycline, marketed as Tygacil by Pfizer, is a twice daily IV, mainly bacteriostatic tetracycline approved for skin infections, pneumonia and intra-abdominal infections. In 2012, revenue worldwide reached $335M. Our conversations with various physicians suggest that use of the drug is hampered by a side effect profile including severe GI toxicity.

**Ceftaroline**. Ceftaroline, launched in 2010 as Teflaro by Forest, is a twice daily IV bactericidal cephalosporin indicated for skin infections and community acquired pneumonia (CAP). The drug is priced five times less than other gram (+) branded drugs, yet is still significantly more expensive than generics, limiting potential sales. Ceftaroline has a run rate of about $55M.

### Drugs in the pipeline

We anticipate three NDAs for gram (+) antibiotics will be filed for approval this year or early next, one of which is dalbavancin.

**Tedizolid**. Tedizolid, like linezolid, is a member of the oxazolidinone class and is available once daily either as an IV injection or an oral pill. Trius has established non-inferiority of tedizolid dosed for six days QD versus linezolid dosed for 10 days BID in two Phase 3 studies (Figure 13). Key competitive advantages over linezolid include 1. the ability to be dosed with MAO inhibitors and 2. a shorter, six-day course of therapy. There are some data suggesting a potential safety advantage over linezolid when

used longer term (i.e., no myelosuppression), which could facilitate usage in indications such as osteomyelitis, but in our opinion, these data need to be further developed. Feedback from key opinion leaders suggests that they are not convinced of the compound's bactericidal feature that management claims for tedizolid given it is in the same class as linezolid, which is known to be bacteriostatic, limiting its use in indications like bacteremia and other infections when bacteremia is suspected. Trius plans to file an NDA later this year, and we anticipate approval by mid-2014. Plans are also underway for a pivotal study in ventilated nosocomial pneumonia later this year.

**FIGURE 13. Summary of Tedizolid Efficacy in Phase 3 Trials ESTABLISH 1&2**

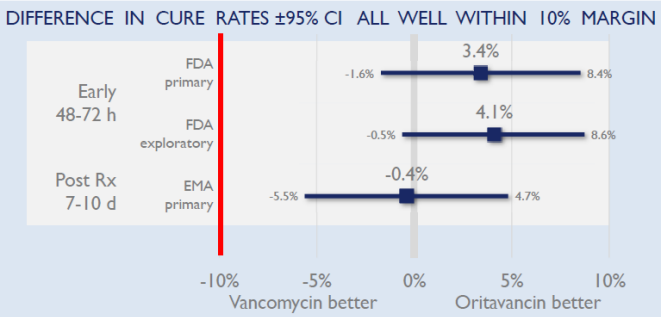
| Endpoint | Study | Tedizolid 6 days treatment, % | Linezolid 10 days treatment, % | Treatment Difference (95% CI), % |
|---|---|---|---|---|
| ≥20% decrease from baseline in lesion area at 48-72 hours | ESTABLISH 2<br>ESTABLISH 1 | 85.2<br>78.0 | 82.6<br>76.1 | 2.6 (-3.0 to 8.2)<br>1.9 (-4.5 to 8.3) |
| Programmatic clinical response at end of therapy | ESTABLISH 2<br>ESTABLISH 1 | 87.0<br>87.0 | 88.0<br>87.8 | -1.0 (-6.1 to 4.1)<br>-0.8 (-5.8 to 4.4) |
| Investigators assessment of clinical response at 7-14 days after end of therapy | ESTABLISH 2<br>ESTABLISH 1 | 88.0<br>85.5 | 87.7<br>86.0 | 0.3 (-4.8 to 5.3)<br>-0.5 (-5.8 to 4.9) |
| Cessation of lesion spread and absence of fever at 48-72 hrs | ESTABLISH 2<br>ESTABLISH 1 | 85.8<br>79.5 | 81.4<br>79.4 | 4.4 (-1.2 to 10.1)<br>0.1 (-6.1 to 6.2) |

*Source: Company reports*

**Oritavancin**. Oritavancin is a bactericidal lipoglycopeptide in development by The Medicines Company with activity against VanA and VanB vancomycin resistant pathogens. The compound has a terminal half-life of 393 hours, or over 16 days, allowing it to be administered as a single dose for skin infections. However, oritavancin also accumulates in macrophages. In 2008, the sponsor Targanta received a complete response letter (CRL) from the FDA requesting additional clinical data in patients with MRSA confirmed pathogens (we estimate about 13%), as well as additional safety data because of the compound's long half-life, higher discontinuation rates and serious adverse events such as sepsis.

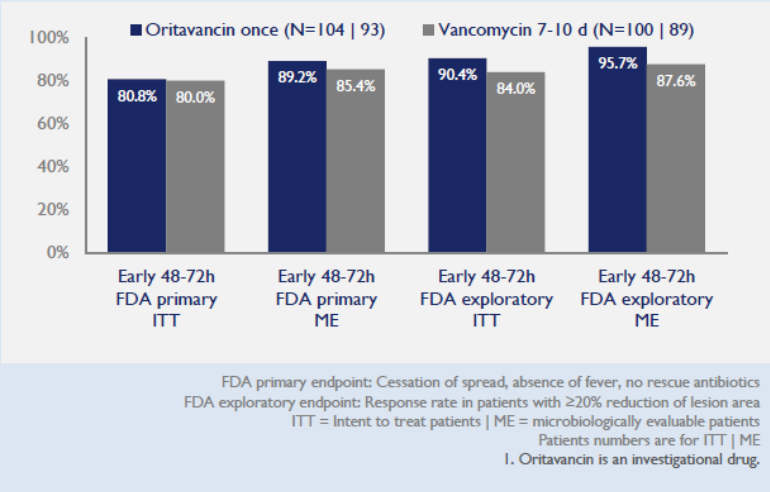
In 2009, The Medicines Company acquired oritavancin and initiated two large 1,000 subject pivotal studies for ABSSSI using the new proposed FDA guidelines. The first study, SOLO-1, was non-inferior to vancomycin (Figure 14) in all patients and in the subset of 21% of patients with confirmed MRSA (Figure 15). Results from SOLO-2 are expected soon. Adverse events were similar between arms and if SOLO-2 is confirmatory, we anticipate the NDA filing in the end of 2013/early 2014 timeframe. We do believe accumulation in macrophages is a regulatory risk and may limit utilization, particularly in indications that requiring long-term dosing, which, in our opinion, is a key market for infrequently administered drugs and we believe a potential source of competitive advantage for dalbavancin over oritavancin. According to our ER physician checks, the 3-hour infusion time could be a disadvantage compared with dalbavancin, which is a 30-minute infusion, because of the desire to free up ER beds.

**FIGURE 14. SOLO-1 Summary of Efficacy Data**




*Source: Company reports*

**FIGURE 15. SOLO-1 Efficacy Data in Confirmed MRSA Subset**




*Source: Company reports*

## Future competition

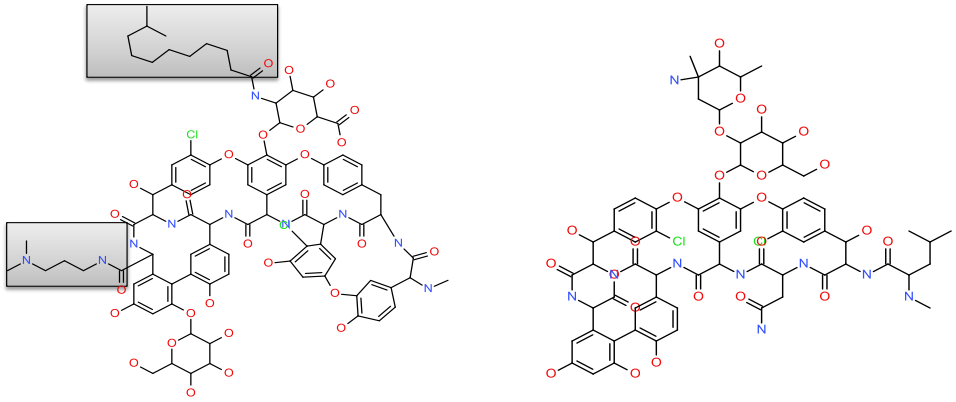
Paratek Pharmaceuticals is developing a broad spectrum semisynthetic tetracycline with activity against MRSA and intends to begin Phase 3 development in skin infections against linezolid this year. Rib-X has initiated a Phase 3 study in skin infections for delafloxicin, a next-generation broad spectrum quinolone with a differentiated resistance profile. Finally, Tetraphase has a broad spectrum synthetic tetracycline with MRSA activity (eravacycline) and we anticipate a Phase 3 program in gram negative infections to start this year, with the potential to expand into the gram (+) market once approved.

## DALBAVANCIN – NOVEL ADDITION TO THE GLYCOPEPTIDE CLASS

Dalbavancin is a member of the glycopeptide class which includes the antibiotic vancomycin and is bactericidal

Dalbavancin is a member of the glycopeptide class which includes the antibiotic vancomycin (Figure 16). Dalbavancin is semisynthetic and considered a "lipoglycopeptide" due to the addition of lipophilic groups which increase the half-life of the compound and confer a resistance profile different than that of vancomycin. The compound works by inhibiting cell wall synthesis by binding to the terminal D-Ala-D-Ala sequence in growing peptidoglycan chains. The affinity for this group is augmented by the lipophilic groups of the molecule via the formation of dalbavancin dimers that anchor the side chains into the membrane of the bacteria, enabling greater potency than vancomycin. It has bactericidal activity.

**FIGURE 16. Structures of Dalbavancin (left) and Vancomycin (right); Lipophilic Groups in Grey**

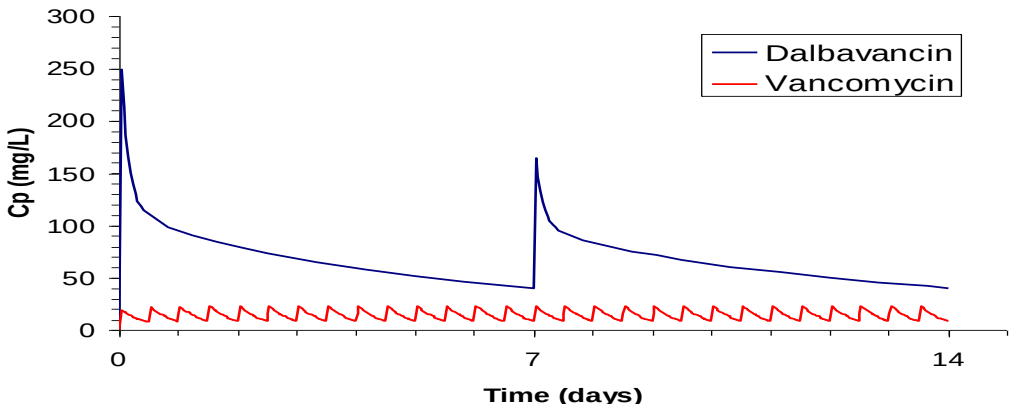


*Source: Company reports and JMP Securities LLC*

Dalbavancin is administered as two 30-minute IV infusions, seven days apart, where the first dose is 1g IV and the second is 500mg IV

Dalbavancin is administered as two 30-minute IV infusions, seven days apart, where the first dose is 1g IV and the second is 500mg IV. The terminal half-life of the drug is 147-258 hours or 6-10 days (Figure 17) with plasma levels above the MIC for most pathogens (misses enterococci) through seven days. Dalbavancin is highly protein bound and is not metabolized by CYP enzymes. Forty percent of the compound is eliminated via the kidneys and most is excreted as intact drug.

**FIGURE 17. PK of Dalbavancin**




*Source: Adapted from JAC 2005; 55 sup S2*

### Strong potency against gram positive infections

Dalbavancin has activity against many gram (+) pathogens (Figure 18). In isolates, its potency is comparable to other gram (+) antibiotics used for MRSA infections: vancomycin, linezolid, and daptomycin. Moreover, dalbavancin is part of the USA surveillance program. The most recent panel including almost 1,600 gram (+) isolates including MRSA and MSSA was from 2012 which was described at this year's ECCMID conference (Figure 19). As expected, dalbavancin demonstrates strong potency against all isolates except for the VanA VRE strains. Importantly, the in vitro potency of the compound has not changed from the first characterization of MIC values in 2002.

**FIGURE 18. In Vitro Potency of Dalbavancin and Vancomycin (mg/L)**

| Bacteria | Dalbavancin | | | Vancomycin | | |
|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | range | $MIC_{50}$ | $MIC_{90}$ | range |
| *Staphylococcus aureus* (MS) | 0.06 | 0.06 | ≤0.008–0.5 | 1 | 1 | 0.25–2 |
| *S. aureus* (MR) | 0.06 | 0.06 | ≤0.008–0.5 | 1 | 2 | 0.25–2 |
| *Staphylococcus epidermidis* (MS) | ≤0.03 | 0.06 | 0.015–0.25 | 2 | 2 | 1–2 |
| *S. epidermidis* (MR) | 0.06 | 0.06 | 0.015–1 | 2 | 4 | 1–4 |
| *Streptococcus pyogenes* (group A) | 0.015 | 0.03 | ≤0.002–0.06 | 0.5 | 1 | 0.5–1 |
| *Streptococcus agalactiae* (group B) | 0.06 | 0.12 | 0.008–0.25 | 0.25 | 0.5 | 0.25–0.5 |
| Other β-haemolytic *Streptococcus* spp. | ≤0.008 | 0.06 | ≤0.002–0.25 | 0.25 | 0.5 | 0.25–1 |
| *Streptococcus pneumoniae* (PS) | 0.015 | 0.03 | ≤0.008–0.06 | 0.25 | 0.5 | 0.06–1 |
| *S. pneumoniae* (PI) | 0.015 | 0.03 | ≤0.008–0.06 | 0.5 | 1 | 0.25–1 |
| *S. pneumoniae* (PR) | 0.015 | 0.03 | ≤0.008–0.25 | 0.25 | 0.5 | 0.06–2 |
| *Enterococcus faecalis* (VS) | 0.03 | 0.06 | 0.015–4 | 1 | 2 | 0.5–4 |
| *E. faecalis* (VR) | 4 | 32 | 0.015–>32 | 512 | 512 | 8 to >512 |
| *Enterococcus faecium* (VS) | 0.06 | 0.12 | ≤0.015–4 | 0.5 | 1 | 0.5–2 |
| *E. faecium* (VR) | 8 | 32 | 0.03–>32 | 512 | 512 | 8 to >512 |
| *E. faecium* (VanA) | 16 | 32 | 0.03–>32 | 512 | 512 | 64 to >512 |
| *E. faecium* (VanB) | 0.03 | 0.12 | 0.03–0.12 | 32 | 64 | 4 to >512 |
| *Clostridium* spp. | 0.03 | 2 | ≤0.015–8 | 0.5 | 1 | 0.25–8 |

MR = methicillin resistant; MS = methicillin susceptible; PI = penicillin intermediate (MIC 0.12-1mg/L); PR = penicillin resistant (MIC ≥ 2mg/L); PS =penicillin susceptible; VR = vancomycin resistant (MIC ≥32mg/L); VS = vancomycin susceptible (MIC≤ 4mg/L)

*Source: Drugs 2010, 70 (7)*

**FIGURE 19. MIC Data Against Gram Positive Pathogens from U.S. in 2012**

| Organism (no. tested) | MIC (mg/L) ≤ 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | > 4 | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Staphylococcus aureus* (1000) | 192 (19.2) | 716 (90.8) | 91 (99.9) | 1 (100.0) | – | – | – | – | – | 0.06 | 0.06 |
| MSSA (500) | 108 (21.6) | 350 (91.6) | 42 (100.0) | – | – | – | – | – | – | 0.06 | 0.06 |
| MRSA (500) | 84 (16.8) | 366 (90.0) | 49 (99.8) | 1 (100.0) | – | – | – | – | – | 0.06 | 0.06 |
| Coagulase-negative staphylococci (122) | 60 (49.2) | 52 (91.8) | 9 (99.2) | 1 (100.0) | – | – | – | – | – | 0.06 | 0.06 |
| MS-CoNS (38) | 24 (63.2) | 13 (97.4) | 1 (100.0) | – | – | – | – | – | – | ≤0.03 | 0.06 |
| MR-CoNS (84) | 36 (42.9) | 39 (89.3) | 8 (98.8) | 1 (100.0) | – | – | – | – | – | 0.06 | 0.12 |
| β-haemolytic streptococci (336) | 308 (91.7) | 21 (97.9) | 4 (99.1) | 3 (100.0) | – | – | – | – | – | ≤0.03 | ≤0.03 |
| Group A Streptococcus (151) | 145 (96.0) | 5 (99.3) | 1 (100.0) | – | – | – | – | – | – | ≤0.03 | ≤0.03 |
| Group B Streptococcus (134) | 118 (88.1) | 11 (96.3) | 3 (98.5) | 2 (100.0) | – | – | – | – | – | ≤0.03 | 0.06 |
| Viridans group streptococci (71) | 60 (84.5) | 10 (98.6) | 1 (100.0) | – | – | – | – | – | – | ≤0.03 | 0.06 |
| *Enterococcus* spp. (60) | 1 (1.7) | 22 (38.3) | 10 (55.0) | 2 (58.3) | 0 (58.3) | 0 (58.3) | 0 (58.3) | 1 (60.0) | 24 (100.0) | 0.12 | >4 |
| vancomycin-susceptible (33) | 0 (0.0) | 22 (66.7) | 9 (93.9) | 2 (100.0) | – | – | – | – | – | 0.06 | 0.12 |
| vancomycin-resistant (27)[a] | 1 (3.7) | 0 (3.7) | 1 (7.4) | 0 (7.4) | 0 (7.4) | 0 (7.4) | 0 (7.4) | 1 (11.1) | 24 (100.0) | >4 | >4 |
| VanA (25) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.0) | 24 (100.0) | >4 | >4 |
| VanB (2) | 1 (50.0) | 0 (0.0) | 1 (100.0) | – | – | – | – | – | – | ≤0.03 | – |

a. Includes: 19 *E. faecium* and six *E. faecalis* isolates with a VanA phenotype and one each of *E. faecium* and *E. faecalis* with a VanB phenotype.

*Source: ECCMID 2013*

### Limited activity against VanA unlikely to limit usage in most infections

In hospitals, there is a growing problem in the increased prevalence of vancomycin-resistant enterococci (VRE). Enterococci are gram (+) anaerobic organisms that primarily present in urinary tract infections, bacteremia, endocarditis, diverticulitis and meningitis. In 2010, 28% of enterococci isolates were resistant to vancomycin. Resistance to vancomycin is the result of resistance genes such as VanA and VanB. Dalbavancin is not potent against VanA, a strain where the D-Ala-D-Ala sequence is altered. In 2007, 76% of VRE isolates in North America and 40% of isolates in Europe were the result of VanA.

The low activity against VanA, in our view, is a concern primarily for bacteremia developing from skin infections, as other enterococci infections are not targets for dalbavancin. To assess the activity of dalbavancin in bacteremia, the drug was evaluated in an open-label, 75-patient Phase 2 study with clinical success rate of 92% on dalbavancin, higher than vancomycin at 45% with 100% of isolated pathogens eradicated by dalbavancin (80% by vancomycin). There were also patients in the DISCOVER studies with bacteremia and management plans to publish on both the Phase 2 study and DISCOVER subset in the next year. Therefore, while we do not think dalbavancin will be a "go to" antibiotic for bacteremia, we do not believe the limited activity against VanA should limit its utilization in infections that could give rise to bacteremia.

## LARGE CLINICAL DATABASE

Five Phase 3 studies evaluating dalbavancin have been conducted

Five Phase 3 studies evaluating dalbavancin have been conducted, including four blinded and one open label in 2,875 patients. A summary of these trials is captured in the chart below (Figure 20). The most recent DISCOVER data have not yet been published or presented at a medical conference, therefore our analysis is limited to the top-line data published by Durata. The totality of the data we have reviewed suggests that dalbavancin has comparable safety and efficacy to currently approved therapeutic options, meeting the benchmark for approval. In our opinion, the key risk in the data set surrounds the relatively low percentage of MRSA cases in the DISCOVER studies (approximately 12% of infections), explained by management as driven by both geographical influences and lesion mix. That being said, we believe the previous clinical data set and recent surveillance data makes the case for efficacy in MRSA and management believes that because dalbavancin is a glycopeptide, known to be active against MRSA, activity in MRSA is not a concern for the FDA.

### Dalbavancin history

Dalbavancin has a long and checkered history with regulators in the U.S. and Europe

Dalbavancin has a long and checkered history with regulators in the U.S. and Europe. Dalbavancin was developed by Vicuron and previously tested in three Phase 3 studies in complicated and uncomplicated skin infections (cSSSI and uSSSI, respectively), establishing the requisite regulatory endpoint of non-inferiority versus commonly used cefazolin in uSSSI and linezolid and vancomycin in cSSSI. In 2005, Vicuron was acquired by Pfizer for $1.9B while the NDA filing for dalbavancin was in process. Unfortunately, three approvable letters from the FDA for dalbavancin were issued in 2005, 2006 and 2007, with the first two citing chemistry manufacturing and control (CMC) issues, and the final a broad shift in FDA thinking on the efficacy endpoint approval of antibiotics for the treatment of skin infections. As such, Pfizer withdrew the NDA in September 2008. In the same year in Europe, the MAA was also withdrawn after the CHMP found the risk benefit profile of dalbavancin to be unfavorable because of the single Phase 3 study, the preponderance of milder infections in the Phase 3 studies in cSSSI and questions about the preclinical safety observations. Durata was incorporated in 2009 for the purposes of purchasing dalbavancin from Pfizer.

At the same time, the FDA clarified its thinking on the issue of skin infections, establishing a new indication, coined ABSSSI (acute bacterial skin and skin structure infections) with a proposed earlier efficacy endpoint to differentiate drugs based on early indicators of resolution of infection, namely reduction of lesion size and absence of fever. After meeting with the FDA in 2010, Durata decided to resubmit the NDA with the old number implying that pre-clinical data would not be reviewed again at NDA submission. Though the FDA requested a single, pivotal study be conducted under the new draft guidelines, Durata conducted two, DISCOVER-1 and -2 under the auspices of a SPA. In Europe, Durata met with the EMA who agreed to accept an MAA filing based on the same data set as the NDA filing, but utilizing the European endpoint of clinical cure at Days 14-15.

## FIGURE 20. Phase 3 Summary

| Indication | | | n | FDA endpoint w/fever (ITT) | FDA endpoint >20% red (ITT) | Clinical response ( EOT); CE | Follow up | % MRSA | MRSA subpopulation FDA endpoint (ITT) | MRSA subpopulation Clinical response ( EOT); CE | MRSA subpopulation Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| cSSSI | VER001-9 | **dalbavancin 1000mg IV (d1); 500mg IV (d8)** | 571 | **88.3%*** | **n/a** | **88.9%** | **n/a** | 22.6% | **n/a** | **96%***** | **n/a** |
| | | linezolid 600mg IV/PO BID, 14d | 283 | 89.6%* | n/a | 91.2% | n/a | 24.7% | n/a | 97%*** | n/a |
| uSSSI | VER001-8 | **dalbavancin 1000mg IV (d1); 500mg IV (d8)** | 367 | **n/a** | **n/a** | **89.1%** | **n/a** | n/a | **n/a** | **n/a** | **n/a** |
| | | cefazolin 500mg IV q8h then oral cephalexin | 186 | n/a | n/a | 89.1% | n/a | | n/a | n/a | n/a |
| MRSA cSSSI** | VER001-16 | **dalbavancin 1000mg IV (d1); 500mg IV (d8)** | 107 | **n/a** | **n/a** | **86%****** | **n/a** | 96% | **n/a** | **89.9%** | **n/a** |
| | | vancomycin IV 100mg BID | 49 | n/a | n/a | 65.3%****** | n/a | | n/a | 86.7% | n/a |
| ABSSSI | DISCOVER-1 | **dalbavancin 1000mg IV (d1); 500mg IV (d8)** | 288 | **83.0%** | **89.6%** | **87.0%** | **93.8%** | 15.3% | **84%** | **86%***** | **n/a** |
| | | vancomycin IV 100mg BID/linezolid 600mg BID PO | 285 | 81.8% | 90.9% | 91.4% | 96.1% | 13.7% | 82% | 97%*** | n/a |
| ABSSSI | DISCOVER-2 | **dalbavancin 1000mg IV (d1); 500mg IV (d8)** | 371 | **76.8%** | **87.6%** | **93.5%** | **96.3%** | 12.4% | **76%** | **98%***** | **n/a** |
| | | vancomycin IV 100mg BID/linezolid 600mg BID PO | 368 | 78.3% | 85.9% | 92.7% | 94.5% | 7.6% | 86% | 100%*** | n/a |

* Post hoc analysis
** open label
*** Microbiological evaluable population
**** ITT population

*Source: Company reports and JMP Securities LLC*

## CLINICAL EFFICACY

### Top-line data establish non-inferiority in line with draft guidance and SPA

In November 2012 and February 2013, Durata reported positive top-line data for DISCOVER-1 and -2, respectively. Full results will be described at the upcoming ICCAC and IDSA meetings in Denver in September and San Francisco in October, respectively, and in the interim, our analysis is based upon top-line data.

DISCOVER-1 and DISCOVER-2 enrolled about 1,321 subjects in the U.S., Canada and Eastern Europe. The study designs were nearly identical: patients were randomized to either dalbavancin (1000mg IV Day 1; 500mg IV Day 8) for the entire duration of therapy or vancomycin (1000mg IV BID) for three days followed by either vancomycin IV BID or linezolid BID PO for the remainder of the 14 days of therapy. The FDA endpoint was non-inferiority for the 'early' composite responder index of cessation of lesion and resolution of fever at 48-72 hours (new FDA proposed endpoint) and the EMA endpoint was the traditional non-inferiority of clinical status at the end of therapy. A non-inferiority margin of 10% was established via SPA and discussions with EU regulators suggest that these data are acceptable for MAA filing.

Both studies met the FDA primary endpoint versus the active control with an 83.0% versus 81.8% and 76.8% versus 78.3% response rate in DISCOVER-1 and DISCOVER-2, respectively

Both studies met the FDA primary endpoint versus the active control with an 83.0% versus 81.8% and 76.8% versus 78.3% response rate in DISCOVER-1 and DISCOVER-2, respectively (Figure 21). Note that lower response rates in DISCOVER-2 may reflect a more severe patient population driven by a higher proportion of patients from eastern European sites (management reported that 60-70% of subjects were from European sites). We also note that because the FDA has not finalized its guidance for the primary endpoint and there has been suggestion that fever may be excluded in the final guidance. Durata prospectively analyzed the data at 48-72 hours without fever and with at least a 20% reduction in lesion size, similarly reaching the non-inferiority hurdle with 89.6% versus 90.0% and 87.6 and 85.9%, respectively.

**FIGURE 21. Early Endpoint Data for DISCOVER (FDA Primary Endpoint)**

| Primary Endpoint (Early Response) | Dalbavancin | Vancomycin/ linezolid | Difference (95% Confidence Interval) |
|---|---|---|---|
| DISCOVER 2 | 285/371 (76.8%) | 288/368 (78.3%) | -1.5% (-7.4, 4.6) |
| DISCOVER 1 | 240/288 (83.3%) | 233/285 (81.8%) | 1.5% (-4.6, 7.9) |
| **Sensitivity analysis (>20% reduction in lesion area at 48-72 hours)** | **Dalbavancin** | **Vancomycin/ linezolid** | **Difference (95% Confidence Interval)** |
| DISCOVER 2 | 325/371 (87.6%) | 316/368 (85.9%) | 1.7% (-3.2, 6.7) |
| DISCOVER 1 | 259/288 (89.9%) | 259/285 (90.9%) | -1.0% (-5.7, 4.0) |

*Source: Company reports*

**FIGURE 22. Clinical Status at Day 14 (EMA Primary Endpoint)**

| Clinical Status D14 | Patient Population | Dalbavancin | Vancomycin/ linezolid | Difference (95% Confidence Interval)[1] |
|---|---|---|---|---|
| DISCOVER 2 | CE | 303/324 (93.5%) | 280/302 (92.7%) | 0.8% (-3.3, 4.9) |
| DISCOVER 1 | CE | 214/246 (87.0%) | 222/243 (91.4%) | -4.4% (-9.6, 1.6) |

*Source: Company reports*

### MRSA subpopulation

In our opinion, the most striking observation in these top-line data is the seemingly lower response rate in the MRSA subpopulation (Figure 23) in DISCOVER-2 at the early endpoint (76% versus 86%) and the lower response in DISCOVER-1 for the European endpoint (86% versus 97%). We believe this may be driven by a small number of subjects with confirmed cases of MRSA since the latest surveillance data does not suggest any migration in susceptibility. Data generated by Vicuron and Pfizer show comparable rates for dalbavancin versus the active control at the end of treatment (Figure 22). Herein lies our primary critique of the top-line data: the proportion of MRSA patients relative to what is seen in the population (60% in the U.S. and 20-25% in Europe, based on literature reports) with only 15% and 14% in DISCOVER-1 and 12% and 8% in DISCOVER-2 for the dalbavancin arms and comparator arms, respectively. This is low relative to the U.S. where about 60% of cases are thought to be MRSA.

Given the small MRSA subset, we think the more appropriate analysis may be to combine the DISCOVER-1 and -2 MRSA data sets. In doing so, we arrive at an 80% versus 84% for FDA endpoint for dalbavancin and vancomycin/linezolid arms, respectively, and 92% versus 98% for the EMA endpoint for the dalbavancin and vancomycin/linezolid arms, respectively, which seem to be with the range of non-inferiority. A critique here is that the small sample size favors a non-inferiority outcome.

**FIGURE 23. MRSA Subset Data**

| MRSA subset: Early Response ITT | Dalbavancin | Vancomycin/linezolid |
|---|---|---|
| DISCOVER 2 | 35/46 (76%) | 24/28 (86%) |
| DISCOVER 1 | 37/44 (84%) | 32/39 (82%) |
| DISCOVER PROGRAM | 72/90 (80%) | 56/67 (84%) |

| MRSA subset: EOT (Day 14) ME* | Dalbavancin | Vancomycin/linezolid |
|---|---|---|
| DISCOVER 2 | 42/43 (98%) | 24/24 (100%) |
| DISCOVER 1 | 30/35 (86%) | 30/31 (97%) |
| DISCOVER PROGRAM | 72/78 (92%) | 54/55 (98%) |
| VER001-9 | 129/135 (96%) | 70/72 (97%) |

*Microbiologically evaluable subset of patients

*Source: Company reports*

Management does not appear concerned by these observations in MRSA for several reasons:

1. It is explained by the higher proportion of patients from Eastern Europe where there is less MRSA – though we note this is still about about half the European rate;

2. Inclusion of more cellulitis lesions, known to be more difficult to treat and where samples to confirm MRSA are rarely possible - though we have not yet seen a breakdown of lesion type in the DISCOVER program;

3. The glycopeptide class is not prone to MRSA resistance – though we note increasing MRSA resistance to another glycopeptide vancomycin;

4. MIC analyses which show high and stable potency against MRSA – a valid argument in our opinion, and finally;

5. MRSA study conducted by Vicuron demonstrating non-inferiority to active control (Figure 23), which we find convincing, particularly considering potency has remained stable.

The key risk, in our view, is the potential for an advisory panel to take issue with the MRSA data set in the current study.

### Prior Phase 3 studies reach non-inferiority hurdle

The key supportive Phase 3 trial from the Vicuron data set is study VER001-9, a double-blind study versus linezolid (started on IV with the option to switch to oral) in the old cSSSI indication. The primary endpoint in the study was clinical response at test of cure (TOC) measured on Day 28. Durata conducted post-hoc analyses of these data, specifically focusing on the subset of patients meeting new ABSSSI inclusion criteria (lesion size >75cm$^2$ or > 50cm2 with fever and elevated immature white blood cell count). These data were analyzed for the new FDA endpoint at 48-72 hours which demonstrated comparable efficacy between dalbavancin and linezolid of 88.3% and 89.6%, respectively (Figure 24). We are encouraged at the consistency of results when compared to the recent DISCOVER trials particularly considering one-quarter of all patients had confirmed MRSA in VER001-9, where 96% and 97% of patients responded using the end of treatment endpoint for dalbavancin and linezolid, respectively. Unfortunately, data using the new endpoint have not been assessed for the MRSA subpopulation in this study.

**FIGURE 24. Post-hoc Analysis of VER001-9 Data (FDA Endpoint)**

Table 5. FDA Primary Outcome Measure: Cessation of Skin Lesion Spread and Afebrile

| Timepoint | Analysis Population | Endpoint | Dalbavancin, n/N (%) | Linezolid, n/N (%) | Difference, 95% CI |
|---|---|---|---|---|---|
| Day 3/4 | Clinically evaluable | Cessation of spread+afebrile | 283/340 (83.2) | 155/178 (87.1) | −3.8 (−10.6, 2.9) |
| | | Cessation of spread | 312/340 (91.8) | 165/178 (92.7) | −0.9 (−6.2, 4.3) |
| | +>75 cm$^2$ lesions* | Cessation of spread+afebrile | 212/258 (82.2) | 109/135 (80.7) | 1.4 (−7.3, 10.1) |
| | | Cessation of spread | 237/258 (91.9) | 121/135 (89.6) | 2.2 (−4.5, 8.9) |
| | +>75 cm$^2$ lesions* + one systemic sign | Cessation of spread+afebrile | 103/135 (76.3) | 67/85 (78.8) | −2.5 (−14.8, 9.7) |
| | | Cessation of spread | 120/135 (88.9) | 76/85 (89.4) | −0.5 (−9.9, 8.9) |
| Day 28 | Clinically evaluable | Clinical response at test of cure | 386/434 (88.9) | 206/226 (91.2) | −2.2 (−7.3, 2.9) |

*Includes facial lesions >50 cm$^2$

*Source: Company reports*

In addition, there was an open-label study in MRSA enrolling 156 patients with cSSSI where the cause was known or suspected to be MRSA. These data were presented in 2005 at ICAAC. Evaluable patients showed a 90% response for dalbavancin at the end of treatment, compared with 87% on vancomycin.

## BEYOND SKIN

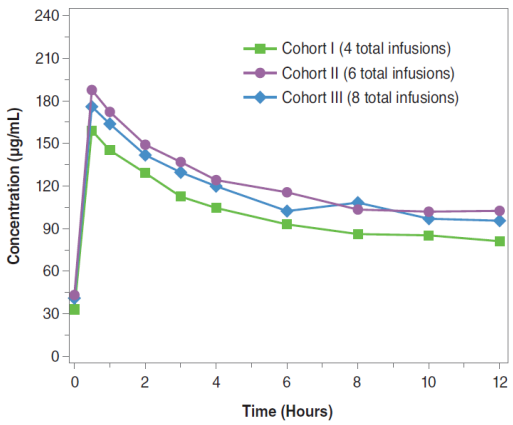
We see opportunities for expansion into infections that could be treated outside the hospital or that require longer duration of therapy which include osteomyelitis, diabetic foot infections, and pneumonia

Antibiotics are generally used more broadly than the FDA approved indication, driven by physician experimentation. Indeed, physician feedback suggests that expansion into additional indications builds confidence in an antibiotic and is an important part of its commercial strategy. Given the profile of dalbavancin with its once-weekly dosing with high potency against common gram (+) pathogens, we see opportunities for expansion into infections that could be treated outside the hospital or that require longer duration of therapy which include osteomyelitis, diabetic foot infections, and pneumonia.

### Osteomyelitis

Osteomyelitis is the infection of bone or bone marrow. Management estimates there are 330,000 cases and 50,000 hospitalizations yearly in the U.S. IDSA guidelines recommend treatment with linezolid, vancomycin or daptomycin for moderate infections for 1-2 weeks of therapy, and with longer (4-8 weeks) treatment for more serious infections. Toward expansion into osteomyelitis, Durata recently presented the results of an eight-week dosing study with dalbavancin dosed at 1000mg IV, followed by 500mg for the following three, five or seven additional weeks with the longest group being exposed to 4,500mg of total dalbavancin. We are encouraged to see that dalbavancin does not accumulate and that mean plasma concentrations were similar after the last 500mg dose, after eight weeks of exposure (Figure 25). Moreover, it appears to be well tolerated after multiple doses with no dose dependent adverse effects (Figure 26). In addition, the company is conducting a bone penetration study and we anticipate data in the late 2013/early 2014 timeframe. Integral to Durata's lifecycle management plans for dalbavancin will be a study in pediatric osteomyelitis, given the pathophysiology of osteomyelitis is more straightforward than for adults. These data, combined with data from the ongoing bone penetration study in adults, in our view, could be sufficient for physicians to begin treating selected osteomyelitis cases with dalbavancin. Given the regulatory uncertainty surrounding this indication, we do not expect Durata to officially pursue approval at this time.

**FIGURE 25. PK Extended Dosing**




*Source: ECCMID 2013*

**FIGURE 26. Treatment emergent adverse events**

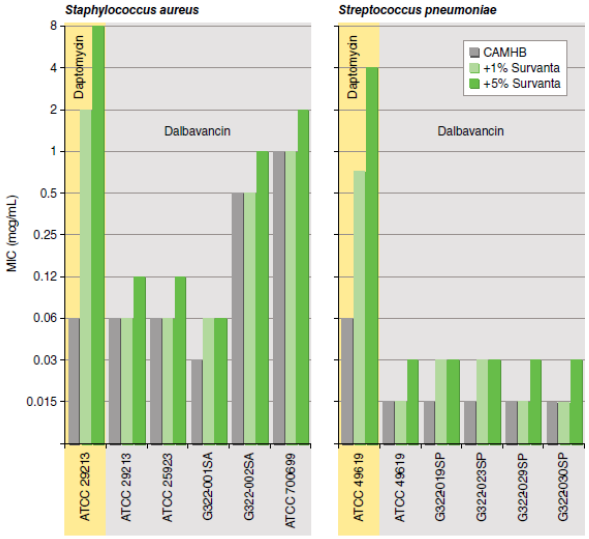
| Adverse Event (AE) | Treatment Arm: Cohort I (n=6) n (%) | Cohort II (n=6) n (%) | Cohort III (n=6) n (%) |
|---|---|---|---|
| Number of subjects with at least 1 TEAE | 2 (33.3%) | 2 (33.3%) | 3 (50.0%) |
| Number of subjects with at least 1 Treatment Related TEAE | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) |
| Pain in extremity | 0 (0.0%) | 1 (16.7%) | 1 (16.7%) |
| Urticaria | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) |

*Source: ECCMID 2013*

### Pneumonia

Unlike daptomycin and oritavancin, the activity of dalbavancin is not reduced by lung surfactant (Figure 27). Therefore, we think dalbavancin may be used in pneumonia. Moreover, dalbavancin shows strong activity against streptococcus pneumonia, suggesting the drug may be a good fit for community acquired pneumonia or CAP, as a once-weekly alternative to what is used empirically in this setting: a respiratory fluoroquinolones or a β-lactam plus a macrolide. With 5.4 million serious (hospitalized) community cases annually, community pneumonia presents a large market, with dalbavancin positioned to avoid hospitalization and where a small penetration could result in meaningful revenue for Durata. Durata plans to conduct a Phase 1 study to evaluate epithelial lining fluid exposures this year and subsequently initiate a study in pneumonia.

**FIGURE 27. Dalbavancin MIC With (Green) and Without (Grey) Surfactant**




*29213, 25923: MSSA resistance; 700699: VISA resistance; 001SA, 002SA: MRSA resistance*

*Source: Company reports, IDSA 2012*

### Diabetic foot infection

With 320,000 cases per year, foot infections are common amongst diabetics. Treatment of up to four weeks is required, making dalbavancin a good fit. Because most infections of this type originate via a wound, typical pathogens are similar to those in skin infections, including MRSA and IDSA, and guidelines recommend empiric therapy against gram (+) enterococci.

## LARGE SAFETY DATABASE AND RECENT LONG-TERM STUDIES MITIGATE RISK

In our view, the large safety database from the current and past trials combined with the recent long-term dosing study support the profile of dalbavancin and should support approval

Because of its long half-life, we believe safety will be a key focus of the regulatory review. In our view, the large safety database from the current and past trials combined with the recent long-term dosing study support the profile of dalbavancin and should support approval. As a reminder, safety was not one of the reasons cited for the approvable letters issued through 2007.

In the recent Phase 3 studies against vancomycin and/or linezolid, the safety profile of dalbavancin was generally in line with previous observations and comparable to the active control. Overall adverse events (through Day 28) were mild and largely gastrointestinal in nature (Figures 28, 29). We are encouraged that these data are consistent with the previous database of over 1,000 people treated with dalbavancin (Figure 30). We remind investors that these recent data are top line and we hope to conduct a more detailed analysis at ICCAC and IDSA later this year.

We are pleased that no difference in mortality has been observed dalbavancin. There was a single death related to an injury. This was deemed a serious adverse event (SAE) observed in the dalbavancin arm of the DISCOVER program, fewer than the seven reported in the vancomycin/linezolid arm. In the early Phase 3 studies, nine patients died in the dalbavancin cohorts compared to seven in the comparator arms. All deaths were found to be unlikely related to the study drug.

**FIGURE 28. Overall Safety Analysis – DISCOVER Program**

| | Dalbavancin | Vancomycin /linezolid |
|---|---|---|
| n | 652 | 651 |
| Adverse event (AE) | 36.5% | 40.2% |
| Treatment emergent AE | 33.1% | 38.1% |
| TEAE onset through d28 | 32.6% | 37.4% |
| TEAE onset after d28 | 4.0% | 7.1% |
| Drug related TEAE | 12.3% | 14.2% |
| TESAE | 2.6% | 4.0% |
| Drug related SAE | 0.3% | 0.6% |
| SAE leading to death | 0.2% | 1.2% |
| TEAE leading to discontinuation | 2.1% | 2.0% |

*Source: Company reports and JMP Securities LLC*

**FIGURE 29. Treatment Emergent Adverse Events Occurring in ≥ 2% of Subjects in DISCOVER Program**

| | Dalbavancin | | Vancomycin/linezolid | |
|---|---|---|---|---|
| | unrelated | related | unrelated | related |
| Patients with at least one TEAE | 19.3% | 12.3% | 21.9% | 14.2% |
| Nausea | 1.7% | 2.5% | 1.3% | 3.1% |
| Headache | 1.7% | 2.1% | 0.4% | 0.2% |
| Pruritis | 0.6% | 2.0% | 0.5% | 1.2% |
| Diarrhea | 0.5% | 1.2% | 0.4% | 1.8% |
| Vomiting** | 1.6% | 0.5% | 0.5% | 0.5% |
| Hypertension* | 2.5% | 0.0% | 2.5% | 0.0% |
| Rash* | 0.7% | 1.1% | 0.4% | 1.8% |
| Asthenia* | 0.4% | 0.0% | 1.8% | 0.4% |

** DISCOVER-1 only; ** DISCOVER-2 only*

*Source: Company reports and JMP Securities LLC*

**FIGURE 30. Phase 2/3 Integrated Database from Previous Studies**

| Preferred Term | Dalbavancin (N = 1126) | Comparator (N = 573) |
|---|---|---|
| ≥ 1 Treatment related AE | 248 (22.0) | 157 (27.4) |
| Diarrhea | 34 (3.0) | 21 (3.7) |
| Nausea | 20 (3.5) | 20 (3.5) |
| GGT increased | 16 (1.4) | 8 (1.4) |
| Rash | 16 (1.4) | 6 (1.0) |
| Vomiting | 14 (1.2) | 6 (1.0) |
| Headache | 13 (1.2) | 8 (1.4) |
| Blood LDH increased | 13 (1.2) | 7 (1.2) |

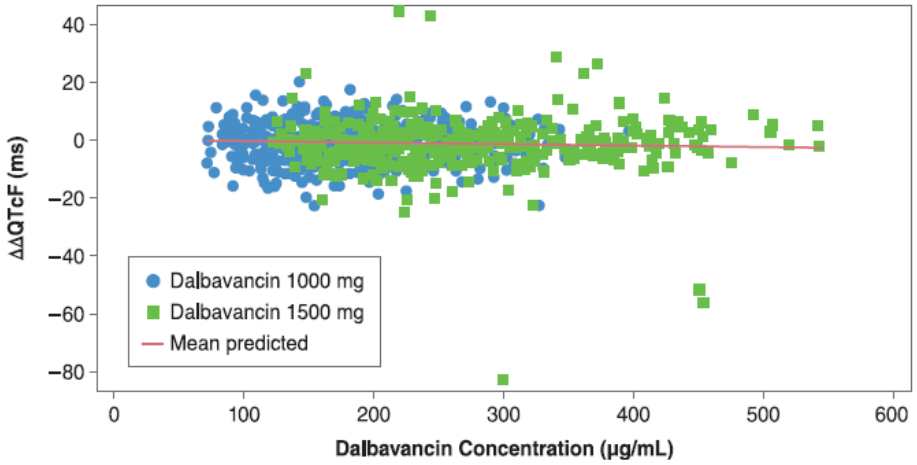
*Source: Company reports*

### QTc data and PK studies supportive of safety profile

As part of a safety workup, Durata conducted pharmacokinetic studies in the elderly and renal impaired patients and while the data have not been fully described, management has relayed that dalbavancin appears well tolerated in these populations and there are no specific changes in PK or safety. We look to conference presentations this fall to analyze these data thoroughly.

Durata also conducted a QTc evaluation for dalbavancin, as other members of the glycopeptide class have been associated with an increase in the QTc interval. Both 1000mg and 1500mg of the drug were given to subjects in a single IV dose given over 30 minutes. 200 patients were enrolled and randomized 1:1:1:1 to a dalbavancin arm, placebo or a positive control, moxiflxacin (Figure 31). The results appear normal. We note that at the high concentration of dalbavancin, one case of red man syndrome (a hypersensitivity reaction caused by histamine release) was observed; however, this is a supra-therapeutic dose and therefore not relevant to clinically relevant doses.

**FIGURE 31. Individual Dalbavancin Concentration vs. ΔΔQTcF with Population Mean Predictions**




Source: *Company reports*

Durata plans to file the NDA in mid-2013

## Regulatory status

Durata plans to file the NDA in mid-2013 and assuming the filing is accepted, we anticipate an advisory committee meeting will be held in 1H14. Dalbavancin received a Qualified Infectious Disease Product (*QDIP*) designation for providing a priority review pathway for the drug. Durata plans to file the MAA in Europe in late 2013 and we estimate a 1-1.5 year review cycle.

## Manufacturing

Active pharmaceutical ingredient (API) is manufactured by Gnosis, a biotechnology company with expertise in semi-synthetic drug manufacturing. As background, Gnosis manufactures teicoplanin, an antibiotic similar to vancomycin. Dalbavancin is made via fermentation and then chemically modified in a manufacturing site in Italy and delivered in powdered form. A second site by Lonza has been also identified. Hospira is responsible for fill and finish and the company plans to bring a second site on eventually. Management has not disclosed how much material they will have on hand heading into launch next year.

We note that both U.S. and EU regulatory authorities identified CMC issues with previous dalbavancin filings. Whereas Europe was mostly concerned about consistency between batches, the FDA noted endotoxin levels (solved by Pfizer) and some quantification methods that management believes have since been addressed. Unfortunately, we have limited visibility into potential CMC issues that may arise this review cycle.

With Hatch-Waxman, we believe dalbavancin is protected through mid-2027

## Intellectual property

The QDIP designation for dalbavancin will provide 10 years market exclusivity in the U.S. The approved patent for dalbavancin is a method of use patent in the U.S. that covers the once-weekly use of the drug and expires in 2024. Assuming the company receives the Hatch-Waxman extension, we believe the company should have market exclusivity through mid-2027. In Europe, the composition of matter patent was filed in 1992 and expires soon, therefore, in Europe, dalbavancin is protected for 10 years after approval by EU data exclusivity rules.

## ROADMAP TO COMMERCIALIZATION

In the U.S., Durata will commercialize the drug itself, whereas outside the U.S., Durata hopes to identify a European partner

Durata intends to commercialize the drug domestically and to identify a European commercial partner. In the U.S., Durata currently has 10 medical science liaison (MSL) directors and four regional business directors on board that are busy building account plans for each target hospital to facilitate formulary access and pull through. Upon approval, we anticipate 100-110 U.S. based sales representatives and 20-30 MSLs and staff will be hired to target 1,900 hospitals in the U.S., of which about 500 account for about 40% of the target opportunity.

The initial set of targets will be on hospitals 'ready to adopt', including many with coordinated discharge centers or EDOUs, before branching out to less ready institutions. Within the hospital, Durata will focus on key stakeholders, including target emergency room directors, pharmacy managers, infectious disease physicians, and 6,000 surgeons and internal medicine physicians who use a high volume of gram (+) antibiotics.

### Where does dalbavancin fit in?

We anticipate skin infections will be the predominate indication for the first several years of launch. As physicians gain comfort with the profile of dalbavancin, we anticipate usage will expand to include other infections requiring longer term therapy, namely, osteomyelitis and diabetic foot ulcers. As a benchmark we point to daptomycin where about 45% of usage is in skin infection – about a $450 million market, where about half is driven by outpatient therapy.

Survey work conducted by Durata suggests that physicians believe about 25% (range 10-50%) of hospital admissions could be avoided by the availability of a more convenient gram (+) treatment option

We think dalbavancin is well-suited for use in the outpatient setting, both OPAT and EDOU. Survey work conducted by Durata suggests that physicians believe about 25% (range 10-50%) of hospital admissions could be avoided by the availability of a more convenient gram (+) treatment option. Emergency room physicians we have spoken are excited about the opportunity to use dalbavancin, believing it can provide a more efficient alternative to vancomycin. We anticipate significant adoption in sophisticated ER settings as dalbavancin's long half-life provides comfort to physicians that there is sufficient drug on board without admitting a patient to the hospital.

As compared to oritavancin, dalbavancin has a short infusion time (30 minutes versus three hours), which would be favored by ER physicians. Moreover, the 7-day second dose fits well with a typical follow-up appointment. Beyond patient satisfaction, which favors outpatient therapy, there are important benefits to treating patients at home, including fewer nosocomial infections and lower costs. While oral options provide a solution for some cases, concerns over onset of activity and compliance continue to support the IV market.

To this point, daptomycin has created significant value in the outpatient setting which drives almost half of its almost $900 million run rate, 50% of which appears to come from complicated and uncomplicated skin infections. We estimate that daptomycin captures $200-$250 million in the outpatient treatment of skin infections with a once daily IV therapy. With a once weekly option, it is conceivable that dalbavancin could both expand the market and compete for share with daptomycin in this setting.

In addition to the outpatient setting, we think dalbavancin may be employed in hospitals to facilitate earlier discharge, particularly in cases where there may be concerns regarding compliance. Bear in mind, that after 2-3 days of inpatient care, hospitals begin to lose money on patients with skin infections and so the hospital is motivated to discharge the patient within this timeframe. Management has indicated that there may be cost savings from using dalbavancin in the hospital driven by less administrative costs, which could offset drug acquisition costs; however, we believe this may be more of a stretch, given that the premium will likely be afforded to dalbavancin over generic alternatives.

Management has described three scenarios of patient flow which impact reimbursement – an important component of decision making when choosing an antibiotic therapy (Figure 32). The first scenario is where we believe Durata will get most traction- with a first infusion in an EDOU and the second in an OPAT (HOPD) setting. Another point of intervention is the second scenario, where dalbavancin is given in the hospital. The primary motivation for this scenario would be a quicker discharge and the potential cost savings, by offsetting the cost of the first infusion which the hospital would incur as part of the bundled payment. The third scenario, where both doses are given in a doctor's office, is less likely in our view, because most serious skin infections are touched by the hospital.

**FIGURE 32. Points of Intervention with Dalbavancin**

| | 1st Infusion | 2nd Infusion |
|---|---|---|
| 1 | Emergency Department (ED) | Hospital Outpatient Department (HOPD) |
| 2 | Inpatient | HOPD / Infusion center |
| 3 | Physician office | Physician office |

**Scenario 1**

- Patients who are released from the ER without being admitted to the hospital inpatient setting are an optimal target population for the drug
  - **Infusion 1** – performed in ED, separate payment for the drug
  - **Infusion 2** – performed in HOPD, separate payment for the drug

**Scenario 2**

- While the inpatient setting is important for the drug, drug costs are bundled into a single payment
  - **Infusion 1** – in inpatient setting, no separate payment for the drug (bundled into DRG)
  - **Infusion 2** – performed in HOPD, separate payment for the drug

**Scenario 3**

- Patients who receive infusions in physician offices are an optimal target population
  - **Infusion 1** – in the physician office, separate payment for the drug
  - **Infusion 2** – in the physician office, separate payment for the drug

*Source: Company reports*

## FINANCIALS

We estimate Durata has about $100 million in cash pro forma after raising $53.5M in 2Q13, which we believe is sufficient to see it through the upcoming regulatory catalysts. Consistent with hospital launches, we estimate the company will reach profitability three years after launch in 2017.

## MANAGEMENT

Durata's management and board have many years of both development and commercial pharmaceutical experience. We believe management has a well thought out strategy of how to successfully launch dalbavancin.

**FIGURE 33. Durata Management Team**

| | Position | Prior affiliations |
|---|---|---|
| Paul Edick | CEO, Director | GANIC Pharma, MedPoint |
| Dr. Michael Dunne | CMO | Pfizer |
| Corey Fishman | CFO | GANIC Pharma, MedPoint |
| John Shannon | COO | Baxter |
| Allison Wey | VP IR | Par Pharma |

*Source: Company reports*

**FIGURE 34. Durata Board of Directors**

| | Position | Affiliations |
|---|---|---|
| Richard De Schutter | Chairman of Board, Incyte | DuPont, Pharmacia, Monsanto, Searle & Co |
| Brent Ahrens | Partner at Canaan Partners | Kalidex, Elevation |
| Paul Edick | CEO, Durata | GANIC Pharma, MedPoint |
| Paul Friedman | CEO, Incyte | DuPont, Merck |
| Lisa Giles | Independent | Searle & Co, Abbott |
| James Healy | Partner Sofinnova Ventures | Anthera, Amarin, Intermune, CoTherix |
| Ron Hunt | MD at NLV Partners | J&J, SmithKliine Beecham |
| Kevin C. O'Boyle | Independent | Advanced BioHealing, NuVasive |
| Nicole Vitullo | Partner at Domain Associates | Achillion, Onyx |

*Source: JMP Securities LLC and Company reports*

## Company Description

Durata is a Chicago-based clinical development company focused on novel therapies for infectious diseases. The company's lead candidate, dalbavancin, is a long-acting IV antibiotic for infections caused by gram positive bacteria, including MRSA. The compound is in Phase 3 development with NDA filing scheduled for this year.

## Investment Risks

Regulatory risk. Durata, like all other drug development companies, is reliant on the FDA's pace of evaluating new drugs and the agency's willingness to approve new drugs. There has recently been a shift in FDA guidance for antibiotics; however, no drugs have yet been approved in conjunction with these new standards. Furthermore, the guidance from the FDA is still in draft form and there are different opinions regarding what the final guidance will be. It is hard to predict what an FDA advisory panel will find when evaluating the data from the clinical studies, which may influence an FDA decision. Durata has limited MRSA data in the current Phase 3 studies which could be a point of discussion and potentially hinder approval. We also note there may CMC issues that we have no visibility to at this point.

Competitive risk. There are other drugs on the market and in development for gram (+) MRSA infections, including Cubist's Cubicin, Pfizer's Zyvox, Trius's tedizolid, and the Medicine Company's oritavancin. There are also two expected generic entrants, generic Zyvox in 2015 and generic Cubicin in 2018 that could make it difficult for dalbavancin to take share.

Commercial risk. Dalbavancin is a hospital-based antibiotic. It may take longer than anticipated for Durata to get dalbavancin on formularies in hospitals, which we see as a key rate limiting factor for the launch. Dalbavancin will be the first antibiotic to be dosed just once weekly and as such, will be forging new ground. Durata may also fail to convince hospitals and physicians of the value proposition for dalbavancin.

Sector risk. Valuation of pharmaceutical stocks is subject to both investor assessments of the prospects of the underlying companies, as well as investor tolerance for risk and confidence in the prospects of pharmaceutical stocks as a group. Therefore, Durata's stock price may fall, even while the company meets or exceeds investor expectations.

Patent risk. Patent expiration can result in a negative impact to sales. Additionally, generic companies may file abbreviated new drug applications to challenge current products with patent protection. Durata is protected by the GAIN act in the U.S. and market exclusivity in the EU that should protect dalbavancin through 2025 at least. If lifecycle management plans are not successful in the interim, generics can come to market after 2025.

## JMP FACTS AND DISCLOSURES

**Analyst Certification:**

The research analyst(s) who prepared this report does/do hereby certify that the views presented in this report are in accordance with my/our personal views on the securities and issuers discussed in this report. As mandated by SEC Regulation AC no part of my/our compensation was, is or will be directly or indirectly related to the specific views or recommendations expressed herein. This certification is made under the obligations set forth in SEC Regulation AC. Any other person or entity may not use it for any other purpose. This certification is made based on my/our analysis on the date of this report's publication. I/We assume no obligation to update this certification to reflect any facts,circumstances or events that may subsequently come to my/our attention. Signed Liisa A. Bayko and Heather Behanna

**JMP Securities Disclosure Definitions:**

JMP Securities currently makes a market in the security of Durata Therapeutics, Inc.

JMP Securities was manager or co-manager of a public offering for Durata Therapeutics, Inc. in the past 12 months.

**JMP Securities Investment Opinion Definitions:**

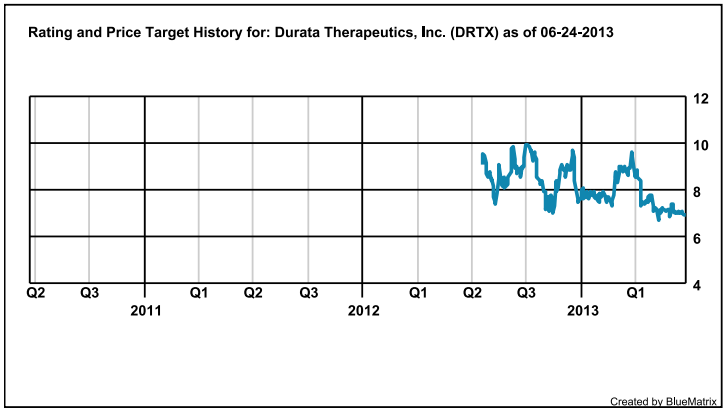
Market Outperform (MO): JMP Securities expects the stock price to outperform relevant market indices over the next 12 months.
Market Perform (MP): JMP Securities expects the stock price to perform in line with relevant market indices over the next 12 months.
Market Underperform (MU): JMP Securities expects the stock price to underperform relevant market indices over the next 12 months.

**JMP Securities Research Ratings and Investment Banking Services:** (as of June 21, 2013)

| JMP Rating | Regulatory Equivalent | # Co's Under Coverage | *% of Total* | Regulatory Equivalent | # Co's Under Coverage | *% of Total* | # Co's Receiving IB Services in Past 12 Months | *% of Co's With This Rating* |
|---|---|---|---|---|---|---|---|---|
| MARKET OUTPERFORM | Buy | 232 | *60.89%* | Buy | 232 | *60.89%* | 74 | *31.90%* |
| MARKET PERFORM | Hold | 143 | *37.53%* | Hold | 143 | *37.53%* | 20 | *13.99%* |
| MARKET UNDERPERFORM | Sell | 6 | *1.57%* | Sell | 6 | *1.57%* | 0 | *0%* |
| TOTAL: | | 381 | *100%* | | 381 | *100%* | 94 | *24.67%* |

**Stock Price Chart of Rating and Target Price Changes:**

Note: First annotation denotes initiation of coverage or 3 years, whichever is shorter. If no target price is listed, then the target price is N/A. In accordance with NASD Rule 2711, the chart(s) below reflect(s) price range and any changes to the rating or price target as of the end of the most recent calendar quarter. The action reflected in this note is not annotated in the stock price chart. Source: JMP Securities.



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