07 January 2014
Americas/United States
Equity Research
Biotechnology

New Antibiotics Expected to Drive Greater Outpatient Use

Research Analysts

Jason Kantor, PhD
415 249 7942
jason.kantor@credit-suisse.com

Jeremiah Shepard, PhD
415 249 7933
jeremiah.shepard@credit-suisse.com

Ravi Mehrotra PhD
212 325 3487
ravi.mehrotra@credit-suisse.com

Lee Kalowski
212 325 9683
lee.kalowski@credit-suisse.com

Koon Ching PhD
212 325 6286
koon.ching@credit-suisse.com

Anuj Shah
212 325 6931
anuj.shah@credit-suisse.com

INDUSTRY PRIMER

Diverse Set of Forces Likely to Increase Size of Outpatient Market

Two forces will likely converge in 2014 to increase the use of new antibiotics: (1) increased cost management and hospital avoidance for patients with skin infections, and (2) the launch of three new antibiotics with similar marketing messages. This industry overview is published in connection with a separate proprietary survey (LINK).

- **Same marketing message from three different companies:** CBST, DRTX and MDCO will be in the market starting in 2014 with similar economic messaging – avoid costly hospitalizations by using more expensive branded drugs that allow for outpatient management. This is key in growing the market for branded drugs where generics are currently entrenched. The efforts of three companies should increase awareness of the potential savings, which is key to driving demand for these products.
- **Long-acting antibiotics can create significant savings for hospitals, but uptake could take time:** Two long-acting antibiotics (dalbavancin from DRTX and oritavancin from MDCO) have had successful Phase III trials, and we expect FDA approval for both in 2014. Dalbavancin requires two IV administrations one week apart (30 minutes each), and oritavancin requires a single IV administration (three hours). Both can potentially prevent or reduce costly hospitalization in appropriate patients (~1/3 of skin infections), generating significant savings relative to traditional IV antibiotics (no in-patient stay, no daily or twice-daily infusions in outpatient setting, etc). That said, we recognize that entrenched interests could cause clinical uptake to take time.
- **Tedizolid offers IV to oral switching:** Tedizolid represents an improved version of the marketed antibiotic Zyvox ($665M in US and $656M exUS in 2012). Importantly, tedizolid has the same IV to oral switching as Zyvox. The IV to oral switch provides another means for reducing in-patient expenses by allowing for more rapid discharge on an oral therapy.
- **Proprietary survey published separately (LINK).** We conducted a survey of 51 doctors regarding potential future use of long-acting antibiotics and tedizolid.
- **We are increasing our target prices** for CBST ($77 from $72) due to using a 4X multiple of 2015 sales instead of 2014 sales and revisions to our antibiotic DCF assumptions; for DRTX ($18 from $15), as we now include 3 additional years of future revenues due to QIDP status; and for MDCO ($45 from $37), with increased value to oritavancin and newly acquired Gram-negative program.

Forces Changing Treatment of Complicated Skin Infections

The current paradigm

Patients with acute bacterial skin and skin structure infections (ABSSSI) most often present in the emergency room. These infections can range from an unexplained red and swollen area to deep surgical or wound infections. Skin infections can present with no other symptoms or with systemic symptoms of fever, high white cell count, and/or sepsis.

- Less complicated cases are typically treated with oral antibiotics.
- More serious cases with systemic symptoms, rapid progression, or other co-morbidities are likely to be treated with IV antibiotics.

Often, patients who are prescribed IV antibiotics will be admitted to the hospital. Sometimes hospital admission is solely for the purpose of administering daily or twice daily IV antibiotics, and sometimes the admission is to monitor treatment progress for a few days. Patients with more complicated infections may be hospitalized for five or more days.

Patients are released from the hospital to receive IV antibiotics at home or in an outpatients infusion center, or are transitioned to orals.

Economic and policy forces are likely to drive changes in ABSSSI treatment

There are structural changes that are driving patient care to the outpatient setting. Below we highlight the factors that will pressure the traditional in-patient IV antibiotic treatment paradigm.

1) **In-patient ward costs most significant part of in-patient treatment:** The largest portion of the costs associated with treating a patient in the hospital is the hospital stay ($1,960/day [2013 Kaiser State Health Facts]; average 4.5 days for ABSSSI; [Stephens et al, ClinicoEconomics and Outcomes Research, 2013]) and non-drug related costs, which can be avoided with outpatient therapy. Many patients are hospitalized solely to administer IV antibiotics but are otherwise healthy. There has been a shift to outpatient care and observation stays versus admissions over the past few years, and we anticipate that this trend will continue, and potentially accelerate with new drug options.

Survey results: Average length of stay was 3.5 days for ABSSSI patients for the 51 docs polled

2) **Hospitals often lose money on diagnosis-related group (DRG) reimbursement.** DRG reimbursement for skin infections is typically insufficient and hospitals lose money on average for patients admitted for IV antibiotic infusions. Long-acting antibiotics administered in the outpatient setting or IV/oral switch can reduce hospital costs. IV antibiotics administered in the outpatient clinic may be reimbursed on a cost plus basis (ASP+6%), providing a profit motive rather than a loss. Additionally, a switch to oral therapy transfers the cost burden away from the hospital, which is a primary driver for oral Zyvox use and future tedizolid use.

3) **Approximately 1/3 of hospitalized ABSSSI patients may not need to be admitted:** Durata estimates that approximately 1/3 of patients admitted for IV antibiotic treatment do not have the characteristics that would require a hospital stay (i.e. co-morbidities), and are admitted for the primary purpose of receiving IV antibiotics. This represents the low hanging fruit for new long-acting antibiotics.

Survey results: The 51 docs indicated that ~30% of their patients are admitted solely for receiving IV antibiotic treatment

4) **Penalties for nosocomial infections:** Penalties for hospital acquired conditions will also push institutions to reduce admissions for patients with infections that lack co-morbidities in order to reduce the incidence of nosocomial infections.

5) **Penalties for Readmissions:** The Hospital Readmissions Reduction Program was enacted on October 2012 and penalizes hospitals for readmissions. This puts pressure on

the hospital to admit fewer patients, and especially those with infections who may be more likely to require readmission.

6) **Accountable Care Organizations (ACO):** These medical providers are incentivized to optimize quality and cost rather than fee for service models. In this structure a more holistic view of treatment cost is considered and may facilitate more hospital-avoiding outpatient treatments.

7) **Antibiotic stewardship programs:** Hospitals and healthcare providers are increasingly focused on the appropriate use of antibiotics to avoid overuse, resistance, and excess costs. If new treatment paradigms are adopted by these programs, it could lead to more rapid adoption of new agents.

Headwinds to change

Challenges to conventional treatment practices are typically met with resistance. For antibiotics, this includes the hospital formulary approval process, existing antibiotic stewardship programs, long-standing clinical practices, and a tendency to save newer agents for later lines of treatment.

We expect that the new antibiotics in 2014 will face the following headwinds:

- **Long-acting antibiotics will require a change in clinical practice:** Current standards of care require daily or twice-daily IV infusions. Physicians can make treatment decisions for these patients daily and consider switching therapies if the response to treatment is suboptimal. A once per week or once-and-done approach is a significant enough change in practice that it could hinder the initial uptake by more conservative physicians.

- **Pricing of the drugs may at first be viewed negatively without greater understanding of the overall savings:** The companies will make the case that the all-in cost of treatment is greatly reduced with a long-acting antibiotic, even if the drug cost is significantly higher. However, cheap generics are likely to remain the mainstay in ABSSSI treatment, and high drug costs could be a barrier to market share gains.

Survey results: 49% of docs indicated that a price of $1000 or higher would be acceptable. We note docs tend to low-ball price, so this is encouraging.

- **New antibiotics tend to have slow adoption curves:** Unlike most therapeutic areas where new drugs are often used first, infectious disease doctors often reserve the newest drugs for patients who fail other drugs. Initial uptake will also be slowed by the formulary approval process in hospitals and complicated decision structures with multiple potential decision makers (ER docs, ID docs, pharmacists, hospital administrators, etc).

- **Physicians may be worried about adverse effects in a long-acting drug:** In clinical trials, the safety data for both dalbavancin and oritavancin are similar to vancomycin. However, physicians may still be concerned that side effect management will be more difficult with long-acting drugs. Education and physician experience are likely to make this concern a nonissue one to two years into launch.

Drug specific caveats that could create additional headwinds

- Dalbavancin requires a second infusion which may be impractical for some patients presenting in the emergency department.

- Oritavancin requires a three hour infusion, which may not be ideal for a busy emergency department focused on getting patients out. The very long half-life of the drug may prevent some physicians away from using the drug.

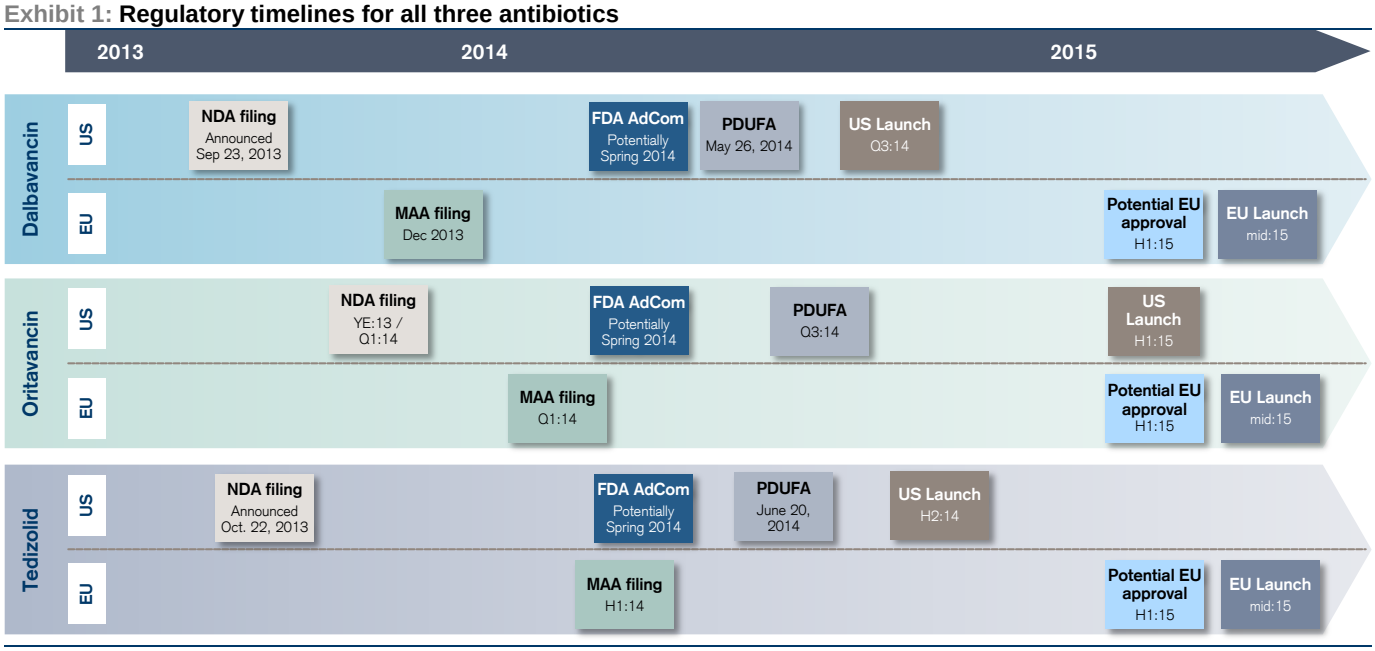
Survey results: ED docs noted a strong preference for once-and-done vs. once per week (88% vs. 12%). ID docs were more evenly split (59% vs. 41%).

- Tedizolid may have some of the same side effects as Zyvox, and a switch to oral treatment has compliance risk. The availability of generic Zyvox potentially in mid:2015 in the US, will likely slow the uptake of tedizolid.

Quick Look at the "Class of 2014" Gram (+) Antibiotics

Dalbavancin, oritavancin and tedizolid will be reviewed for approval in 2014 (Exhibit 1). The PDUFA date for dalbavancin is May 26, tedizolid is June 20, and oritavancin will likely be in Q3:14. Dalbavancin and oritavancin are both glycopeptides and are most similar to vancomycin (Exhibit 2). Tedizolid is an oxazolidinone and most similar to Zyvox (Exhibit 3). We group them together as the "class of 2014" in this report because of the timing of their launch and the likely similarity of their marketing messages (hospital avoidance).

Exhibit 1: Regulatory timelines for all three antibiotics



Source: Company data, Credit Suisse estimates

Long-acting antibiotics: Dalbavancin and oritavancin

Dalbavancin and oritavancin represent a new class of IV drugs with unusually long half-lives, which have the potential to move treatment out of the hospital and into the outpatient setting. Dalbavancin has a shorter half-life than oritavancin. It is dosed with a convenient 30 minute infusion on day 1 and then again on day 8. Oritavancin has a longer half-life and can be dosed as a single 3 hour IV infusion. Both are ideal for use in the emergency department without the need to admit patients to the hospital.

Dalbavancin and oritavancin have both completed multiple Phase III trials in ABSSSI. Other potential indications include pneumonia, osteomyelitis, and diabetic foot infections. Long-acting antibiotics may be particularly well suited for chronic infections such as osteomyelitis, which often require months of treatment.

Exhibit 2: Overview of the profile for long-acting antibiotics relative to vancomycin

	Dalbavancin	Oritavancin	Vancomycin
ROA	IV	IV	IV
Dosing	30 min infusion on day 1 and 8	3 hour infusion one time only	Twice daily with continuous trough level monitoring
Activity	Bactericidal	Bactericidal	Bactericidal
Class of molecule	Glycopeptide	Glycopeptide	Glycopeptide
Potential for extended dosing	Yes, up to 8 wks	Repeated dosing unclear because of long residence time	Yes
Other potential indications	Pneumonia, osteomyelitis, diabetic foot infections	Prosthetic joint infections, bacteremia, and endocarditis	Numerous Gram (+) indications

Source: Company data, Credit Suisse estimates

Tedizolid

Tedizolid belongs to the oxazolidinone class of antibiotics (like Pfizer's Zyvox). This class is differentiated in that it offers IV to oral switching due to high bioavailability. This dosing strategy provides for the flexibility of IV treatment in the hospital with the ability discharge patients on oral treatment. While the mode of administration and treatment paradigm is different relative to long-acting antibiotics, the marketing push is likely to be similarly focused on the economics of hospital cost avoidance.

Survey results: Docs appeared willing to use

Because of its similarity to Zyvox, there will be fewer initial barriers to market tedizolid, but with the likely entrance of generic Zyvox in the coming years, tedizolid will face increased challenges to adoption.

A key point of differentiation versus Zyvox includes a shorter six-day course and once daily dosing relative Zyvox with ten days of twice daily dosing. A differentiated side effect profile may also be reflected in the label, though that remains to be seen. The Phase III studies demonstrated that tedizolid has an improved hematological profile relative to Zyvox (Exhibit 3).

CBST is conducting a Phase III study of tedizolid vs. Zyvox in pneumonia (HAP/VAP). The trial was scheduled to start in December 2013. This 726-patient study will test for non-inferiority in all-cause mortality.

Exhibit 3: Overview of the profile for tedizolid relative to linezolid

	Tedizolid	Zyvox (linezolid)
ROA	IV or oral	IV
Dosing	Daily dosing of IV or oral formulation for 6 days (200 mg/day)	Twice daily dosing of IV or oral formulation for 10-14 days (1200 mg/day)
Activity	Bactericidal	Bacteriostatic
Class of molecule	Oxazolidinone	Oxazolidinone
Potential for extended dosing	Yes	Limited by myelosuppression
Potential for pneumonia indication	Phase III to start by YE:13	Approved for HAP and CAP
Other indications	TBD	Approved for vancomycin-resistant E. faecium infections, including concurrent bacteremia; uncomplicated skin infections

Source: Company data, Credit Suisse estimates

Efficacy: Non-inferiority to standard of care

All three antibiotics recently completed Phase III studies that demonstrated non-inferiority to standard comparators in ABSSSI (Exhibit 4). Oritavancin was compared to vancomycin; dalbavancin was compared to vancomycin with the potential to switch to oral Zyvox; and tedizolid was compared to Zyvox.

Exhibit 4: Efficacy results for the recent Phase III studies

	Dalbavancin	Vanc/Zyvox		Oritavancin	Vanc		Tedizolid	Linezolid
US Primary endpoint (48-72 hours)			**US Primary endpoint (48-72 hours)**			**US Primary endpoint (48-72 hours)**		
DISCOVER-1	83.3%	81.8%	SOLO-1	82.3%	78.9%	ESTABLISH-1 (Oral only)	79.5%	79.4%
DISCOVER-2	76.8%	78.3%	SOLO-2	80.1%	82.9%	ESTABLISH-2 (IV to Oral)	85.8%	81.4%
≥20% reduction in lesion size			**≥20% reduction in lesion size**			**≥20% reduction in lesion size**		
DISCOVER-1	89.9%	90.9%	SOLO-1	86.9%	82.9%	ESTABLISH-1 (Oral only)	78.0%	76.1%
DISCOVER-2	87.6%	85.9%	SOLO-2	85.9%	85.3%	ESTABLISH-2 (IV to Oral)	85.2%	82.6%
EMA Primary endpoint (7-14 days)			**EMA Primary endpoint (7-14 days)**			**EMA Primary endpoint (7-14 days)**		
DISCOVER-1	87.0%	91.4%	SOLO-1	79.6%	80.0%	ESTABLISH-1 (Oral only)	85.5%	86.0%
DISCOVER-2	93.5%	92.7%	SOLO-2	82.7%	80.5%	ESTABLISH-2 (IV to Oral)	88.0%	87.7%

US primary endpoint = Cessation of spread, absence of fever, and no rescue antibiotics.

EMA primary endpoint = Investigator-assessed clinical cure.

Source: Company data, Credit Suisse estimates

Durata likely to make the case that its patients were sicker

The patients enrolled in the DISCOVER-1 and -2 trials were generally sicker than those enrolled in oritavancin's SOLO-1 and SOLO-2 trials (Exhibit 5). While this does not change the overall conclusion of either clinical program, DRTX is likely to use this as a point of differentiation. Specifically, more patients were enrolled with fever (~85% vs. 14-24%), with larger lesion size (~350 cm^2 vs 250-290 cm^2), and with signs of systemic infection (SIRS: 40-60% vs 15% in SOLO-1; NA for SOLO-2).

Exhibit 5: Comparison of Disease Severity in SOLO and DISCOVER Trials

Patient Characteristic	SOLO-1		SOLO-2		DISCOVER-1		DISCOVER-2	
	Oritavancin	Vancomycin	Oritavancin	Vancomycin	Dalbavancin	Vanco/Linezolid	Dalbavancin	Vanco/Linezolid
	N=475	N=479	N=503	N=502	N=288	N=285	N=371	N=368
Fever	14.3%	16.5%	23.5%	21.2%	85.6%	85.2%	83.8%	84.9%
Median Lesion size (cm2)	248.0	225.6	287.8	308.8	333.0	367.8	313.5	362.4
MRSA patients	104	100	100	101	35	31	43	24
SIRS	15.6%	15.1%	NA	NA	61.6%	61.6%	42.7%	43.8%

Source: Company data, Credit Suisse estimates

MDCO is likely to point to its efficacy in MRSA

In many cases where IV antibiotics are used for ABSSSI, the target organism is drug-resistant staph (MRSA).

The SOLO-1 and SOLO-2 trials enrolled a large number of MRSA patients (N=405 total) and the efficacy was essentially identical between the arms for both the US and EU primary endpoints. In a pooled subset analysis from SOLO-1 and SOLO-2 oritavancin was statistically better than vancomycin for the more stringent endpoint of reducing lesion size ≥20% at 48-72 hours (Exhibit 6). While this data may not make it into the FDA approved label, MDCO expects to publish these results, which could be utilized in a marketing campaign for the drug.

DRTX enrolled fewer MRSA patients in DISCOVER-1 and -2 (N=133 total) and the efficacy results in this subgroup were therefore more variable. There were nonsignificant numerical differences in favor of the control group for the EMA endpoint in DISCOVER-1 and the FDA endpoint in DISCOVER-2. However, we believe that the variability between the groups in the arms was likely due to small MRSA patient numbers in these studies.

Exhibit 6: MRSA subset analyses for dalbavancin and oritavancin

MRSA pts	N=133		MRSA pts	N=405	
	Dalbavancin	Vanc/Zyvox		Oritavancin	Vanc
US Primary endpoint (48-72 hours)			**US Primary endpoint (48-72 hours)**		
DISCOVER-1	84.1%	82.1%	SOLO-1	80.8%	80.0%
DISCOVER-2	76.1%	85.7%	SOLO-2	82.0%	81.2%
			≥20% reduction in lesion size		
			SOLO-1	90.4%	84.0%
			SOLO-2	96.0%	90.1%
EMA Primary endpoint (7-14 days)			**EMA Primary endpoint (7-14 days)**		
DISCOVER-1	85.7%	96.8%	SOLO-1	82.7%	83.0%
DISCOVER-2	97.7%	100.0%	SOLO-2	84.0%	85.1%

Source: Company data, Credit Suisse estimates

Economics and Pricing

Hospital avoidance is key for premium value-based pricing

Both DRTX and MDCO have presented separate pharmcoeconomic analyses for costs associated with ABSSSI treatments. The IV antibiotic most frequently used in the hospital setting by patient share is vancomycin and by dollar value is Cubicin. These two therapies are administered as an in-patient or started as in-patient and then continued in the outpatient setting.

- DRTX has conducted an analysis for IV antibiotics in the in-patient and outpatient setting. Vancomycin treatment with five days of in-patient treatment followed by nine days of outpatient treatment costs approximately $13,000, while Cubicin treatment with the same in-patient and outpatient split costs about $16,000. If a patient is administered dalbavancin in the outpatient setting at a cost of approximately $3,000 there is still substantial savings.
- MDCO has completed its own analysis and estimates that a four day in-patient stay with 6 days of outpatient treatment costs approximately $7,750 for vancomycin. Nearly all of that cost can be avoided with oritavancin (~$7,300). This provides a wide range of options for value based pricing and a sharing of the savings between the payor and MDCO.

The key takeaway message is that long-acting antibiotics can potentially generate significant savings with an outpatient treatment with one or two infusions. The DRTX analysis also highlights that meaningful savings (to the healthcare system) can be realized from avoiding repeated outpatient visits as well (though outpatient visits are a profit center given the current reimbursement model).

Exhibit 7: DRTX and MDCO pharmacoeconomic analyses of IV therapy costs

	DRTX estimates			MDCO estimates	
Key assumptions					
Drug	Dalbavancin	Vancomycin	Daptomycin	Oritavancin	Vancomycin
In-patient days	NA	5 days in-patient	5 days in-patient	NA	4 days in-patient
Out-patient days	Day 1, 8	9 days out-patient	9 days out-patient	Once and done	6 days out-patient
Drug in-patient	NA	~100	~1400	NA	180
Drug out-patient	~3000	~200	~2500	TBD	270
In-patient medical	NA	~9700	~9700	NA	6173
Out-patient medical	~900	~3000	~2500	415	1128
Total costs	$3,896	$13,022	$16,083	$415 + Orit cost	$7,751

MDCO estimates adjusted to fit format.

Source: Company data, Credit Suisse estimates

Pricing of the new antibiotics

We believe that both MDCO and DRTX are going use value based pricing for oritavancin and dalbavancin. This means calculating the total savings to the hospital and splitting that savings between a higher drug price (to the company) and some amount of cost savings to the hospital/provider (incentive; Exhibit 7). As a reference, MDCO and DRTX may also look at the full cost for a course of branded antibiotics, such as Cubicin (Exhibit 8).

From our conversations with management and our analysis of their presentations, we conclude that DRTX is likely to price dalbavancin more in-line with a full course of Cubicin

therapy (around $3,000). MDCO has been less clear and their presentations have some inconsistencies. MDCO's pricing decision may be influenced by the price of dalbavancin, which is expected to launch first. We do not expect MDCO to aggressively compete on price and expect the message for both drugs will be around the value to the hospital/provider.

Our conclusions from our work on the potential pricing of the long-acting antibiotics are the following:

Survey results: 49% of docs indicated that a price of $1000 or higher would be acceptable. We note docs tend to low-ball price, so this is encouraging.

(1) While the companies may have hinted at price ranges, this remains an undetermined variable

(2) A price of ~$3,000 per course of treatment seems defendable

(3) MDCO has had success with value based pricing with Angiomax, and we expect it to pursue a similar tact with oritavancin pricing

(4) MDCO has suggested that it will not try to undercut DRTX on price, but will compete on differences on the product profile - we do not expect a large price difference between the two products.

(5) It is unclear if MDCO will choose to price oritavancin relative to the first dose of dalbavancin or both doses

(6) In addition to the cost saving messaging, there may be incentives (ASP +6%) to use higher priced drugs to the outpatient setting

For reference, we have included the pricing for approved therapies per recommended course of therapy in ABSSSI (Exhibit 8).

Exhibit 8: Current pricing for approved therapies in ABSSSI

Drug price analysis	Cubicin - IV	Zyvox - IV	Zyvox - oral	Tygracil	Teflaro	Vibativ
Price (Unit size)	$319 (500mg)	$60 (600mg)	$117 (600mg)	$61 (50mg)	$57 (600mg)	$299 (750mg)
Recommend dose	4 mg/kg QD	600 mg/BID	600 mg/BID	50 mg/ BID	600 mg/BID	10 mg/kg QD
Recommended Duration	7-14 days	10-14 days	10-14 days	5-14 days	5-14 days	7-14 days
5 days	NA	NA	NA	$613	$575	NA
7 days	$2,231	NA	NA	$858	$805	$2,093
10 days	$3,187	$1,203	$2,340	$1,225	$1,150	$2,990
14 days	$4,462	$1,684	$3,275	$1,715	$1,609	$4,186

Source: Company data, Credit Suisse estimates

DRTX – Value based pricing

Based on prior presentations, we believe that DRTX is considering an average cost of ~$3,000 per therapy (Exhibit 9), which is comparable to the drug cost for 10 days of Cubicin therapy.

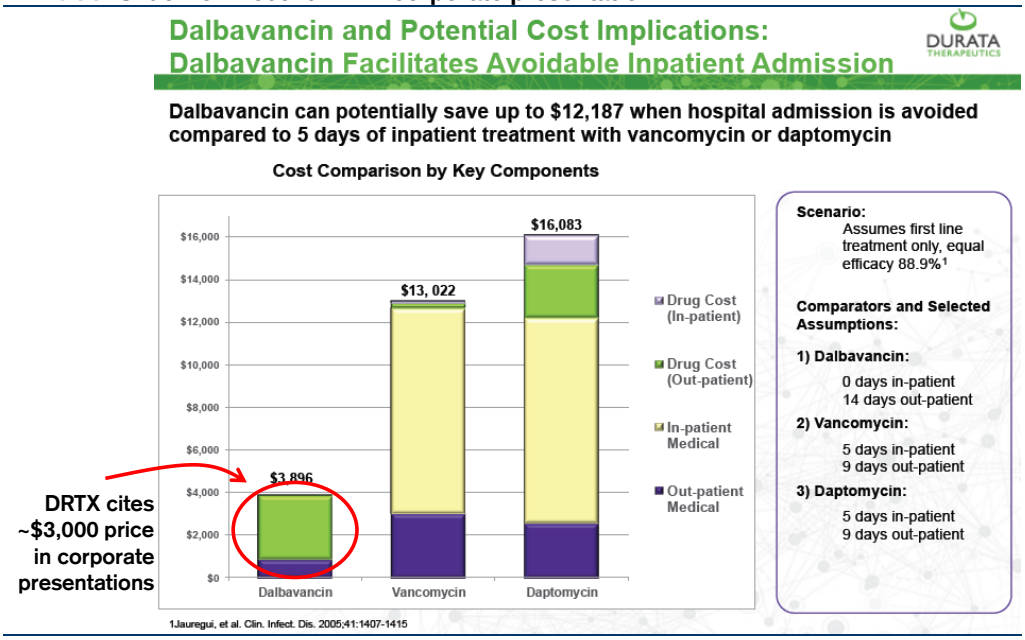
- The first dose is twice the size as the second dose, and thus will be priced proportionally. If 100% of the patients were to receive the second dose, then the ~$3,000 price would be split $2,000 for the first dose and $1,000 for the second dose. However, it is unlikely that all patients will receive the second dose.
- If we assume (as we believe DRTX is) that approximately 50% of patients will receive the second dose, then the ~$3,000 price would be split $2,400 for the first dose and

$1,200 for the second dose to for an average cost of $3,000 per treatment (Exhibit 10).

A high price for the first infusion will likely be an impediment to adoption for hospitalized patients (reimbursed under a fixed DRG). However, the price is likely more reasonable if hospitalization can be avoided, and in the outpatient setting, clinics may charge ASP+6% for dalbavancin, providing additional profits.

DRTX is doing extensive market research and already has a team of 20 MSLs/marketing team members interacting with decision makers at the top ~500 hospitals.

Exhibit 9: Slide from recent DRTX corporate presentation



Source: DRTX corporate presentation 2013

Exhibit 10: Potential pricing for dalbavancin

	Price	Realized price if 100% receive 2nd dose	Price	Realized price if 50% receive 2nd dose
1st dose	$2,000	$2,000	$2,400	$2,400
2nd dose	$1,000	$1,000	$1,200	$600
Total	$3,000	$3,000	$3,600	$3,000

Source: Company data, Credit Suisse estimates

MDCO – Value-based pricing

MDCO is most likely to price oritavancin based on the projected savings to hospitals. However, its peak sales estimate seems to imply a much lower price. We do not expect MDCO will offer oritavancin at a steep discount to dalbavancin or an equivalent course of Cubicin.

Value-based pricing

Value based pricing would imply that MDCO will price based on a percentage of the savings that it can offer to hospitals. Given its estimated cost savings of approximately $7,000 (Exhibit 7), MDCO could price at $3,000 and still offer significant savings to payors. A higher price point could also be supported, in our opinion.

Given MDCO will launch after DRTX, it is unclear how it will price oritavancin relative to dalbavancin. It could price at a premium to the first infusion of dalbavancin and offer the convenience and additional savings of no second infusion. We believe that the value based pricing model will be MDCO's primary determinant of price (MDCO's stated strategy), while it also is likely to offer oritavancin at a discount to the all-in cost of the two infusions of dalbavancin (our assumption).

Backing into price

At its analyst event on October 9, MDCO disclosed key assumptions to arrive at its >$400M peak sales estimate for oritavancin. MDCO expects to reach these sales with 19.8% share of a 1.5 to 2.1M eligible patient market that is expected to grow 1% each year (Exhibit 11).

Using these estimates, we were able to back into a range of potential prices for a patient pool in 10 years. If you take the mid-point for the eligible patient population (1.8M), we arrive at a $1,000 price point (Exhibit 12).

We believe the oritavancin market share estimate is too high, which artificially deflates the price estimate. We believe that MDCO is likely to charge a meaningfully higher price than ~$1,000.

Exhibit 11: **Slide from MDCO presentation at Investor and Analyst Day**

Parameter	Assumptions
ABSSSI patients	1,500,000-2,100,000 patients
Patient growth	1% per year
Dose	1,200mg once only dose
Peak market share	19.8% average across all classes
Value-based pricing opportunity	Up to $2,065-$7,372
Exclusivity	Through 2025
Revenue at peak	More than $400,000,000 per year

Source: MDCO corporate presentation 2013

Exhibit 12: **Potential pricing for oritavancin**

Key assumptions (per MDCO)		Est. pts now	1.8M pts
Patients	1.5M to 2.1M	Pts in 10 yrs	1,988,320
Peak penetration	19.8%	Penetration	19.8%
Peak sales	$400M	Price est.	$1,016

Source: Company data, Credit Suisse estimates

CBST likely to charge premium for tedizolid relative to Zyvox

Tedizolid is differentiated from Zyvox in that it caused less hematological toxicities (Exhibit 13) in the two Phase III studies and may be less likely cause resistance. We believe that CBST will be able to charge a premium relative to Zyvox based on this profile. We have assumed that CBST charges a 20% premium to the price of Zyvox for a 10-day course of

therapy (we assume a 5% price increase for Zyvox from current levels in early 2014). We assume that this cost will be distributed over the 6-day course of therapy for tedizolid (Exhibit 14).

Additionally, there is preclinical evidence that suggests that tedizolid could have a significantly reduced chance for serotonin effects (Flanagan *et al*, Antimicrobial Agents and Chemotherapy; July 2013, Vol 57:No. 7, pp 3060-3066). It is unclear if this difference will be reflected in the label. We assume a larger clinical program would be needed to demonstrate this difference.

Establishing a differentiated profile in the market based on product attributes (vs. Zyvox) and not price will be key for CBST as generic Zyvox (potentially in 2015) would likely take substantial share and limit long term upside for tedizolid.

Exhibit 13: Platelet analysis of tedizolid vs linezolid in ESTABLISH 1 & 2 studies

Laboratory results	Tedizolid N(%)	Zyvox (linezolid) N(%)	p-value
Study Day 7-9 - # of patients	554	551	
Below LLN	18 (3.2%)	31 (5.6%)	0.05885
Below 75% of LLN	8 (1.4%)	12 (2.2%)	0.378
Study Day 11-13 - # of patients	552	537	
Below LLN	27 (4.9%)	58 (10.8%)	0.0003
Below 75% of LLN	7 (1.3%)	20 (3.7%)	0.0106
Last dose of active drug - # of patients	546	520	
Below LLN	20 (3.7%)	56 (10.8%)	<0.0001
Below 75% of LLN	9 (1.6%)	17 (3.3%)	0.1114
Any post-baseline through last dose of active drug	627	626	
Below LLN	27 (6.4%)	54 (12.6%)	0.0002
Below 75% of LLN	6 (2.1%)	21 (4.5%)	0.0175

Source: Company data, Credit Suisse estimates

Exhibit 14: Potential pricing for tedizolid

	Actual WAC cost NOW		CS estimated 2014 WAC cost	
Drug price analysis	Zyvox - IV	Zyvox - oral	Tedizolid - IV	Tedizolid - oral
Price per day	$120	$234	$253	$491
Dose in cSSSI (mg/kg)	600 mg/BID	600 mg/BID	200 mg/QD	200 mg/QD
Recommended Duration	10-14 days	10-14 days	6 days	6 days
6 days	NA	NA	$1,516	$2,948
10 days	$1,203	$2,340	NA	NA
14 days	$1,684	$3,275	NA	NA

20% premium

Source: Company data, Credit Suisse estimates

Fragmented market likely to expand with new entrants

Oritavancin and dalbavancin should help expand the market

The biggest opportunities for new long-acting antibiotics are to take share from generic vancomycin, which accounts for approximately 70% of the current market, and from Cubicin's outpatient business, which accounts for approximately ~50% of Cubicin sales.

Since long-acting antibiotics are a new paradigm in the treatment of ABSSSI (weekly or single-infusion antibiotic versus daily infusion), we believe that having two drugs entering the market at the same time will be beneficial in accomplishing the relatively difficult task of changing clinical practice. We believe that the greatest opportunity will come from avoiding hospitalization or reducing the number of infusions needed in an outpatient setting.

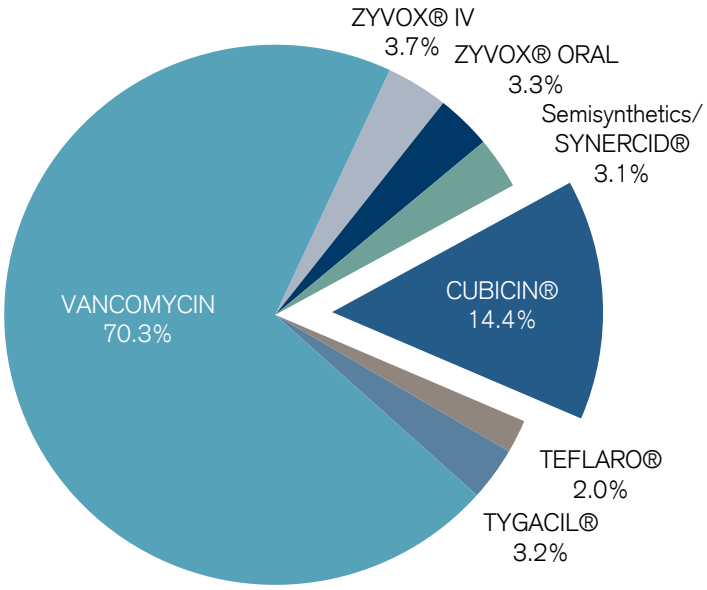
Survey results: ED docs noted a strong preference for once-and-done vs. once per week (88% vs. 12%). ID docs were more evenly split (59% vs. 41%).

The launch of these products should proceed like other antibiotic launches, which generally progress at a steady pace from launch through the life of the product. We estimate that this new class of drugs could conservatively capture between 10% to 30% of the market over many years (for comparison, Cubicin has 14%), which at current Cubicin pricing would be approximately $575M to $1.7B per year. Our current projections for dalbavancin and oritavancin conservatively estimate ~$700M in US sales by 2020.

Fragmented Market for Gram-Positive Antibiotics

Generic vancomycin has the large majority of the Gram-positive antibiotic market, with approximately 70% share of total days of IV antibiotics (Exhibit 15). The overall branded Gram-positive antibiotic space generated U.S. sales of over $1.6B in 2012 (Exhibit 16). At Cubicin pricing, each percentage of market share is worth approximately $58M in net sales. The overall market shares are likely to change in the next few years with (1) several new branded IV antibiotics (listed in Exhibit 17), and (2) the introduction of generic Zyvox.

Exhibit 15: Gram-Positive Market Analysis Based on Days of Therapy



Note: CBST reported that Cubicin had 14.0% market share for the 12 months ending August 2013.
Source: Company data, Credit Suisse estimates.

Exhibit 16: Marketed Gram-Positive Therapeutics

Name	Company	ROA	Dosing	Activity	Class of molecule	CY2012 US Sales	Indication
Vancomycin	GENERIC	IV	2X / day	Static	Glycopeptide	NA	cSSSI, endo, bone, LRTI, septicemia
Cubicin (daptomycin)	CUBIST PHARMACEUTICALS	IV	1X / day	Bactericidal	Lipopeptide	$809.2M	cSSSI, SAB/RIE
Zyvox (linezolid)	Pfizer	IV / oral	2X / day	Static	Oxazolidinone	$665.0M	cSSSI, HAP, CAP, uSSSI, DFI, VRE
Tygacil (tigecycline)	Pfizer	IV	2X / day	Mostly static	Tetracycline	$152.2M	cSSSI, cIAI, CAP HAP, VRE, DFI (Phase III completed)
Teflaro (ceftaroline)	CEREXA / Forest Laboratories, Inc.	IV	2X / day	Bactericidal	Cephalosporin	$38.8M	cSSSI, CABP
Ceftobiprole	basilea PHARMACEUTICA	IV	2X or 3X / day	Bactericidal	Cephalosporin	$0M	Approved only in EU for CAP, HAP
Vibativ (telavancin)	Theravance	IV	1X / day	Bactericidal	Lipoglycopeptide	$0M	cSSSI, HAP/VAP

Source: Company data, Credit Suisse estimates.

Exhibit 17: Therapeutics in Late-Stage Development

Name	Company	ROA	Dosing	Activity	Class of molecule	Status	Indication
Dalbavancin	DURATA THERAPEUTICS	IV	1X / week	Bactericidal	Glycopeptide	2 Positive Ph3 trials; PDUFA May 26, 2014; MAA filed Dec 2013	ABSSSI
Oritavancin	THE MEDICINES COMPANY	IV	1 dose total	Bactericidal	Glycopeptide	2 Positive Ph3 trials; NDA expected YE:13/Q1:14; MAA in H1:14	ABSSSI
Tedizolid	CUBIST PHARMACEUTICALS	IV / oral	1X / day	Bactericidal	Oxazolidinone	2 Positive Ph3 trials; PDUFA June 20, 2014; MAA H1:14	ABSSSI
Delafloxacin	Melinta THERAPEUTICS	IV / oral	2X / day	Bactericidal	Fluoroquinolone	Phase III PROCEED started May 2013	ABSSSI
Omadacycline	PARATEK PHARMACEUTICALS	IV / oral	1X / day	Bactericidal	Aminomethylcycline	Phase III with SPA expected to begin soon	ABSSSI and CABP

Source: Company data, Credit Suisse estimates.

FDA – A Checkered Past, but Significantly Improved Environment

There are few therapeutic areas that have had a more difficult road with FDA than drugs for complicated skin infections. In fact, most of the drugs expected to be approved by the FDA over the next two years were previously rejected or substantially delayed by FDA.

The result is that many of the drugs in late-stage development have traded hands one or more times, as the original sponsors ultimately gave up, and the programs were acquired by companies willing to rerun large Phase III programs.

- **Dalbavancin** was originally taken to Phase III by Vicuron, which was acquired by Pfizer in December 2009. After three approvable letters from FDA, Pfizer ultimately divested the program to Durata, which subsequently re-ran the Phase III program and recently reported two positive Phase III trials.
- **Oritivancin** was taken into Phase III by InterMune. After failing to win FDA approval, the program was acquired by Targanta, which attempted to gain approval without running additional Phase III trials. The Medicines Company acquired Targanta and subsequently re-ran the Phase III program, and it recently reported positive data for the two Phase III trials.
- **Tedizolid** was developed by Trius, who took a risk in being the first company to run a Phase III using newly established but unproven clinical endpoints for FDA approval. It ran its two Phase III trials sequentially rather than in parallel because of limited financial resources. Following two positive Phase III trials, Trius was ultimately acquired by CBST in July 2013.

FDA Changed Guidelines for Phase III Trials

When Cubicin was approved in 2003 for complicated skin and soft-tissue infections (cSSTI), the primary endpoint was clinical cure rate at the test of cure date, which was typically 10-14 days after starting therapy. Subsequently, FDA began to question multiple aspects of skin infection trial design, including (1) the noninferiority margins, (2) the entry criteria, and (3) the clinical endpoint.

The result has been a complete overhaul of the regulatory process to include:

- A new definition of complicated skin infections is now called acute bacterial skin and skin structure infection (ABSSSI). The enrollment criteria for Phase III trials were defined more specifically to limit the number of patients with certain types of infections.
- New primary endpoints for Phase III trials focus on shorter-term outcomes. Rather than defining success as clinical cure at the completion of treatment, success is now measured by cessation of spread or reduction in the size of the lesion in the first two to three days of treatment. This new endpoint required new tools to reproducibly measure lesion size. This endpoint is still in flux, and it is different from the accepted endpoint in Europe, which remains the clinical cure rate after treatment.
- A clear definition of noninferiority is now 10%. Prior trials tested a range of outcomes from 10% to 15%. FDA 10% noninferiority is appropriate.

New Endpoints Were Initially a Risk but Are Now Well Validated

When these regulatory changes were first suggested and adopted by companies that were running new Phase III programs, there was substantial risk that the new endpoints would not replicate the positive data seen in previous trials or that the new endpoints would not correlate well with established endpoints.

Trius was the first company to complete a Phase III trial with the new endpoints. Subsequently, Durata and The Medicines Company have both completed Phase III trials with the new endpoints. Each company measured lesion size in slightly different ways, but the clear finding is that the new lesion size endpoint replicated previous Phase III results and correlated with the previous standard endpoints (which are now secondary endpoints).

GAIN Act Provides New Incentives for Antibiotic Development

In addition to the FDA providing better guidance for the development of antibiotics for treating skin infections, Congress passed new legislation in 2012 (GAIN Act) to promote the development of new antibiotics. The Act set up the qualified infectious disease product (QIDP) designation that is granted to antibiotics in specific indications.

Exhibit 18: Comparison of QIDP status for each antibiotic

	Dalbavancin	Oritavancin	Tedizolid
Indications with QIDP	ABSSSI	ABSSSI	ABSSSI & HABP/VABP
IP (before extensions)	2023	2015	2026
Exclusivity with QIDP	2025	2025	2025

Source: Company data, Credit Suisse estimates

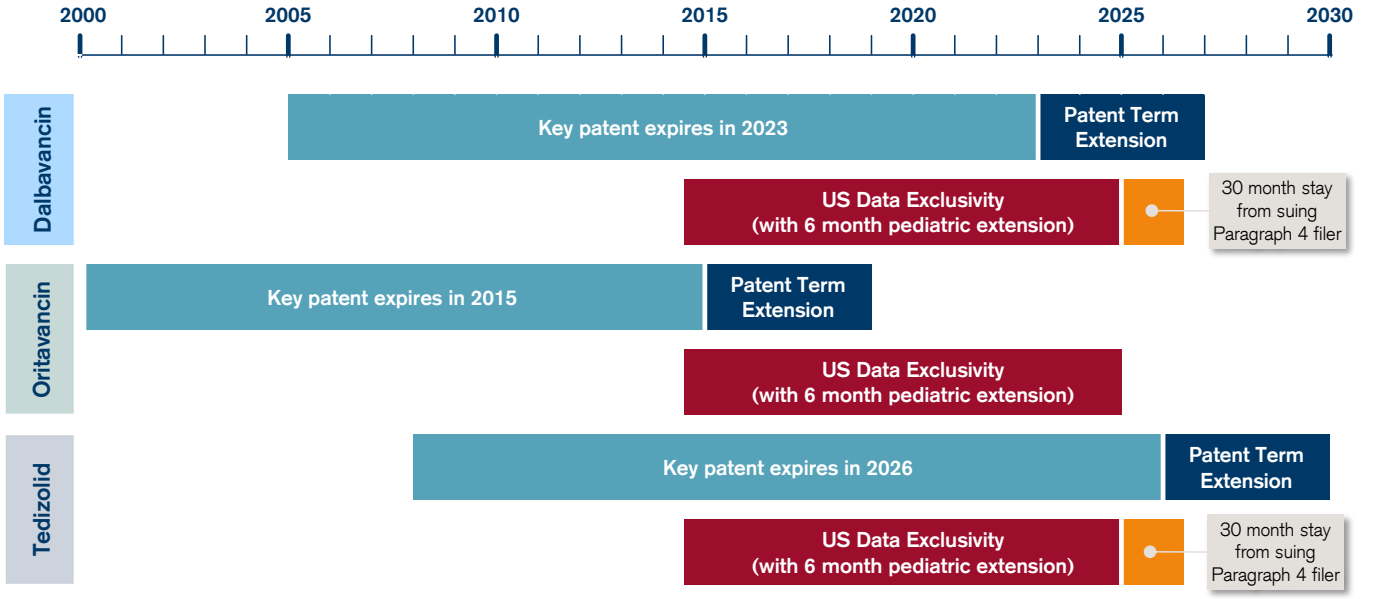
The QIDP provides antibiotic drug developers with two key incentives:

- **Five Years of Additional Market Exclusivity in Addition to the Five Years Already Provided under Hatch-Waxman:** We believe this is the most significant portion of the legislation. For drugs with little or no patent protection, this provision may provide the necessary incentive to run trials to seek approval. For drugs with adequate patent protection, this provision delays potential Paragraph IV challenges by generics. A Paragraph IV challenge can be made one year prior to the end of data exclusivity which is in year four for most drugs and now year nine for drugs with the QIDP designation. This is unique to antibiotic development.
- **FDA Priority Review Potentially Shortens Review Period to Six Months:** The six-month review clock potentially means that drugs could reach the market quicker. While FDA has not done a great job completing review on time for other drugs with priority review, priority reviews are still quicker on average than standard reviews.

The QIDP designation also makes the drugs eligible for "fast track" status. However, it is unclear what the significance of this status at the terminal part of the clinical development. This might help facilitate additional discussions, but does not seem as meaningful as the Priority review.

The GAIN Act also calls for the FDA to develop new guidelines for the development of antibiotics to treat multidrug-resistant infections. These clinical/regulatory pathways will be developed for each indication and could provide drug developers with faster paths to market in more limited indications with high unmet medical need. These new pathways are likely to be tested first for some of the emerging Gram (-) antibiotics that target highly resistant pathogens.

Exhibit 19: Estimated exclusivity and patent protection for the three antibiotics



Source: Company data, Credit Suisse estimates

Company	Price ccy	Price 06 Jan 14	Rating* Prev.	Rating* Cur.	Target Price Prev.	Target Price Cur.	Year End	EPS Ccy	EPS FY1E Prev.	EPS FY1E Cur.	EPS FY2E Prev.	EPS FY2E Cur.	EPS FY3E Prev.	EPS FY3E Cur.
Cubist Pharmaceuticals (CBST)	US$	67.20	—	O	72.00	77.00	Dec 12	US$	—	(0.57)	—	(0.19)	0.95	0.98
Durata Therapeutics (DRTX)	US$	12.44	—	O	15.00	18.00	Dec 12	US$	—	(2.70)	(2.61)	(2.48)	(0.60)	(1.08)
The Medicines Company (MDCO)	US$	37.74	—	O	37.00	45.00	Dec 12	US$	—	0.46	0.59	0.60	2.84	3.06

**O – Outperform, N – Neutral, U – Underperform, R – Restricted* *[V] = Stock considered volatile (see Disclosure Appendix).*
Source: Company data, Credit Suisse estimates.

CREDIT SUISSE

Companies Mentioned *(Price as of 06-Jan-2014)*

AstraZeneca (AZN.L, 3598.5p)
Basilea Pharmaceutica Ltd. (BSLN.S, SFr108.0)
Cubist Pharmaceuticals (CBST.OQ, $67.2, OUTPERFORM, TP $77.0)
Durata Therapeutics (DRTX.OQ, $12.44, OUTPERFORM[V], TP $18.0)
Eli Lilly & Co. (LLY.N, $51.53)
Forest Laboratories Inc. (FRX.N, $58.47)
Johnson & Johnson (JNJ.N, $92.33)
Novartis (NVS.N, $79.19)
Pfizer (PFE.N, $30.55)
The Medicines Company (MDCO.OQ, $37.74, OUTPERFORM, TP $45.0)
Theravance Inc. (THRX.OQ, $35.81)

Disclosure Appendix

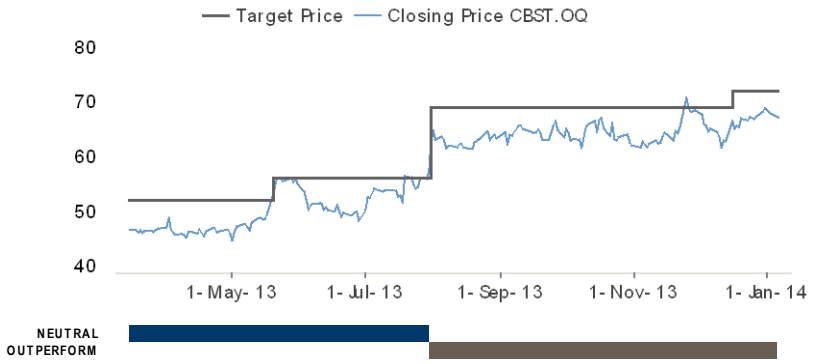
Important Global Disclosures

Jason Kantor, PhD, Ravi Mehrotra PhD and Lee Kalowski each certify, with respect to the companies or securities that the individual analyzes, that (1) the views expressed in this report accurately reflect his or her personal views about all of the subject companies and securities and (2) no part of his or her compensation was, is or will be directly or indirectly related to the specific recommendations or views expressed in this report.

3-Year Price and Rating History for Cubist Pharmaceuticals (CBST.OQ)

CBST.OQ	Closing Price	Target Price	
Date	(US$)	(US$)	Rating
15-Mar-13	46.56	52.00	N *
20-May-13	53.48	56.00	
31-Jul-13	62.33	69.00	O
16-Dec-13	66.51	72.00	

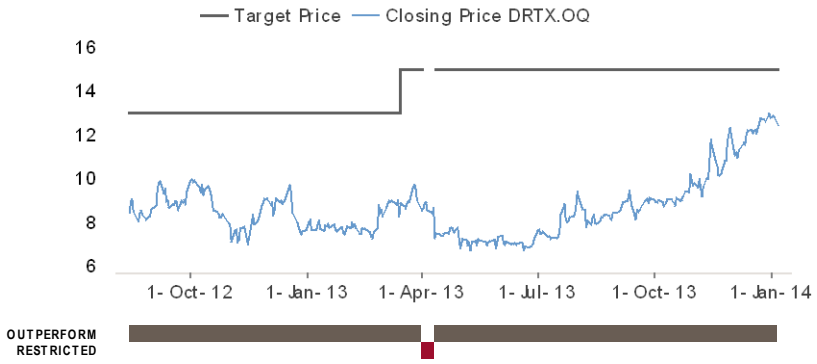
** Asterisk signifies initiation or assumption of coverage.*



3-Year Price and Rating History for Durata Therapeutics (DRTX.OQ)

DRTX.OQ	Closing Price	Target Price	
Date	(US$)	(US$)	Rating
14-Aug-12	8.44	13.00	O *
15-Mar-13	8.85	15.00	*
01-Apr-13	8.52		R
12-Apr-13	7.49	15.00	O

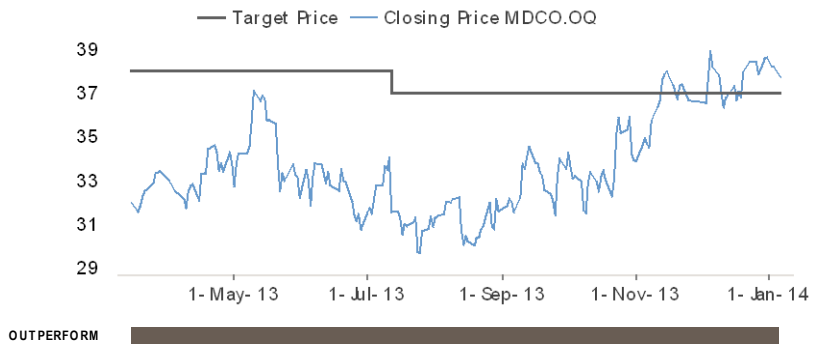
** Asterisk signifies initiation or assumption of coverage.*



3-Year Price and Rating History for The Medicines Company (MDCO.OQ)

MDCO.OQ	Closing Price	Target Price	
Date	(US$)	(US$)	Rating
15-Mar-13	31.97	38.00	O *
12-Jul-13	31.56	37.00	

** Asterisk signifies initiation or assumption of coverage.*



The analyst(s) responsible for preparing this research report received Compensation that is based upon various factors including Credit Suisse's total revenues, a portion of which are generated by Credit Suisse's investment banking activities

As of December 10, 2012 Analysts' stock rating are defined as follows:

Outperform (O) : The stock's total return is expected to outperform the relevant benchmark*over the next 12 months.

Neutral (N) : The stock's total return is expected to be in line with the relevant benchmark* over the next 12 months.

Underperform (U) : The stock's total return is expected to underperform the relevant benchmark* over the next 12 months.

**Relevant benchmark by region: As of 10th December 2012, Japanese ratings are based on a stock's total return relative to the analyst's coverage universe which consists of all companies covered by the analyst within the relevant sector, with Outperforms representing the most attractive, Neutrals the less attractive, and Underperforms the least attractive investment opportunities. As of 2nd October 2012, U.S. and Canadian as well as European ratings are based on a stock's total return relative to the analyst's coverage universe which consists of all companies covered by the analyst within the relevant sector, with Outperforms representing the most attractive, Neutrals the less attractive, and Underperforms the least attractive investment opportunities. For Latin American and non-Japan Asia stocks, ratings are based on a stock's total return relative to the average total return of the relevant country or regional benchmark; Australia, New Zealand are, and prior to 2nd October 2012 U.S. and Canadian ratings were based on (1) a stock's absolute total return potential to its current share price and (2) the relative attractiveness of a stock's total return potential within an analyst's coverage universe. For Australian and New Zealand stocks, 12-month rolling yield is incorporated in the absolute total return calculation and a 15% and a 7.5% threshold replace the 10-15% level in the Outperform and Underperform stock rating definitions, respectively. The 15% and 7.5% thresholds replace the +10-15% and -10-15% levels in the Neutral stock rating definition, respectively. Prior to 10th December 2012, Japanese ratings were based on a stock's total return relative to the average total return of the relevant country or regional benchmark.*

Restricted (R) : In certain circumstances, Credit Suisse policy and/or applicable law and regulations preclude certain types of communications, including an investment recommendation, during the course of Credit Suisse's engagement in an investment banking transaction and in certain other circumstances.

Volatility Indicator [V] : A stock is defined as volatile if the stock price has moved up or down by 20% or more in a month in at least 8 of the past 24 months or the analyst expects significant volatility going forward.

Analysts' sector weightings are distinct from analysts' stock ratings and are based on the analyst's expectations for the fundamentals and/or valuation of the sector* relative to the group's historic fundamentals and/or valuation:

Overweight : The analyst's expectation for the sector's fundamentals and/or valuation is favorable over the next 12 months.

Market Weight : The analyst's expectation for the sector's fundamentals and/or valuation is neutral over the next 12 months.

Underweight : The analyst's expectation for the sector's fundamentals and/or valuation is cautious over the next 12 months.

**An analyst's coverage sector consists of all companies covered by the analyst within the relevant sector. An analyst may cover multiple sectors.*

Credit Suisse's distribution of stock ratings (and banking clients) is:

Global Ratings Distribution

Rating	Versus universe (%)	Of which banking clients (%)
Outperform/Buy*	43%	(53% banking clients)
Neutral/Hold*	40%	(49% banking clients)
Underperform/Sell*	15%	(43% banking clients)
Restricted	2%	

**For purposes of the NYSE and NASD ratings distribution disclosure requirements, our stock ratings of Outperform, Neutral, and Underperform most closely correspond to Buy, Hold, and Sell, respectively; however, the meanings are not the same, as our stock ratings are determined on a relative basis. (Please refer to definitions above.) An investor's decision to buy or sell a security should be based on investment objectives, current holdings, and other individual factors.*

Credit Suisse's policy is to update research reports as it deems appropriate, based on developments with the subject company, the sector or the market that may have a material impact on the research views or opinions stated herein.

Credit Suisse's policy is only to publish investment research that is impartial, independent, clear, fair and not misleading. For more detail please refer to Credit Suisse's Policies for Managing Conflicts of Interest in connection with Investment Research: http://www.csfb.com/research and analytics/disclaimer/managing_conflicts_disclaimer.html

Credit Suisse does not provide any tax advice. Any statement herein regarding any US federal tax is not intended or written to be used, and cannot be used, by any taxpayer for the purposes of avoiding any penalties.

Price Target: (12 months) for Cubist Pharmaceuticals (CBST.OQ)

Method: Our $77 target price is calculated using a 4.0x multiple of our 2015 revenue forecast and a sum of the parts DCF valuation. The high multiple is justified based on greater revenue diversity, increased sales synergy, offset costs for the European expansion, and greater future top-line growth opportunities.

Risk: Risks to our $77 Target Price include: 1) Expectation that CXA-201 will receive US and EU approval in a timely manner, 2) Execution risk associated with the build out of the EU infrastructure, 3) New competitor drug sales could cut into Cubicin growth, and 4) Potentially reduced profitability over the next few years as the company ramps up clinical development and the EU build-out.

Price Target: (12 months) for Durata Therapeutics (DRTX.OQ)

Method: Our $18 TP for DRTX is derived from a revenue multiple analysis of dalbavancin revenues by applying a 3.0X multiple to our 2017 revenue forecast of $231M, discounted back at 12% and a DCF of dalbavancin revenues through 2027.

Risk: Key risk factors to our $18 TP include: 1) dalbavancin is not approved or the launch is significantly delayed, 2) dalbavancin launch ramp and/or peak sales underperforms our estimates, and 3) dalbavancin is not broadly adopted for other MRSA indications.

Price Target: (12 months) for The Medicines Company (MDCO.OQ)

Method: We arrive at our $45/share target price using a 3.4X multiple of our 2015 revenue estimate and a sum-of-the-parts DCF, in which we assign $14/share for Angiomax, $4/share for other marketed products, $25/share for the pipeline, and $2/share for its net cash.

Risk: Risks to our $45 Target Price include: 1) Timing of generic threat to Angiomax is unresolved and could negatively impact the stock if it comes in 2015 instead of 2019, 2) Generic erosion for Angiomax is made worse by multiple entrants, and 3) Relatively short patent life for its pipeline could limit the peak revenues of products that reach the market.

Please refer to the firm's disclosure website at https://rave.credit-suisse.com/disclosures for the definitions of abbreviations typically used in the target price method and risk sections.

See the Companies Mentioned section for full company names

The subject company (DRTX.OQ) currently is, or was during the 12-month period preceding the date of distribution of this report, a client of Credit Suisse.

Credit Suisse provided investment banking services to the subject company (DRTX.OQ) within the past 12 months.

Credit Suisse has managed or co-managed a public offering of securities for the subject company (DRTX.OQ) within the past 12 months.

Credit Suisse has received investment banking related compensation from the subject company (DRTX.OQ) within the past 12 months

Credit Suisse expects to receive or intends to seek investment banking related compensation from the subject company (CBST.OQ, DRTX.OQ, MDCO.OQ) within the next 3 months.

As of the date of this report, Credit Suisse makes a market in the following subject companies (CBST.OQ, DRTX.OQ, MDCO.OQ).

Important Regional Disclosures

Singapore recipients should contact Credit Suisse AG, Singapore Branch for any matters arising from this research report.

The analyst(s) involved in the preparation of this report have not visited the material operations of the subject company (CBST.OQ, DRTX.OQ, MDCO.OQ) within the past 12 months

Restrictions on certain Canadian securities are indicated by the following abbreviations: NVS--Non-Voting shares; RVS--Restricted Voting Shares; SVS--Subordinate Voting Shares.

Individuals receiving this report from a Canadian investment dealer that is not affiliated with Credit Suisse should be advised that this report may not contain regulatory disclosures the non-affiliated Canadian investment dealer would be required to make if this were its own report.

For Credit Suisse Securities (Canada), Inc.'s policies and procedures regarding the dissemination of equity research, please visit http://www.csfb.com/legal_terms/canada_research_policy.shtml.

CREDIT SUISSE

Credit Suisse has acted as lead manager or syndicate member in a public offering of securities for the subject company (DRTX.OQ) within the past 3 years.

As of the date of this report, Credit Suisse acts as a market maker or liquidity provider in the equities securities that are the subject of this report.

Principal is not guaranteed in the case of equities because equity prices are variable.

Commission is the commission rate or the amount agreed with a customer when setting up an account or at any time after that.

For Credit Suisse disclosure information on other companies mentioned in this report, please visit the website at https://rave.credit-suisse.com/disclosures or call +1 (877) 291-2683.

CREDIT SUISSE

References in this report to Credit Suisse include all of the subsidiaries and affiliates of Credit Suisse operating under its investment banking division. For more information on our structure, please use the following link: https://www.credit-suisse.com/who_we_are/en/This report may contain material that is not directed to, or intended for distribution to or use by, any person or entity who is a citizen or resident of or located in any locality, state, country or other jurisdiction where such distribution, publication, availability or use would be contrary to law or regulation or which would subject Credit Suisse AG or its affiliates ("CS") to any registration or licensing requirement within such jurisdiction. All material presented in this report, unless specifically indicated otherwise, is under copyright to CS. None of the material, nor its content, nor any copy of it, may be altered in any way, transmitted to, copied or distributed to any other party, without the prior express written permission of CS. All trademarks, service marks and logos used in this report are trademarks or service marks or registered trademarks or service marks of CS or its affiliates. The information, tools and material presented in this report are provided to you for information purposes only and are not to be used or considered as an offer or the solicitation of an offer to sell or to buy or subscribe for securities or other financial instruments. CS may not have taken any steps to ensure that the securities referred to in this report are suitable for any particular investor. CS will not treat recipients of this report as its customers by virtue of their receiving this report. The investments and services contained or referred to in this report may not be suitable for you and it is recommended that you consult an independent investment advisor if you are in doubt about such investments or investment services. Nothing in this report constitutes investment, legal, accounting or tax advice, or a representation that any investment or strategy is suitable or appropriate to your individual circumstances, or otherwise constitutes a personal recommendation to you. CS does not advise on the tax consequences of investments and you are advised to contact an independent tax adviser. Please note in particular that the bases and levels of taxation may change. Information and opinions presented in this report have been obtained or derived from sources believed by CS to be reliable, but CS makes no representation as to their accuracy or completeness. CS accepts no liability for loss arising from the use of the material presented in this report, except that this exclusion of liability does not apply to the extent that such liability arises under specific statutes or regulations applicable to CS. This report is not to be relied upon in substitution for the exercise of independent judgment. CS may have issued, and may in the future issue, other communications that are inconsistent with, and reach different conclusions from, the information presented in this report. Those communications reflect the different assumptions, views and analytical methods of the analysts who prepared them and CS is under no obligation to ensure that such other communications are brought to the attention of any recipient of this report. CS may, to the extent permitted by law, participate or invest in financing transactions with the issuer(s) of the securities referred to in this report, perform services for or solicit business from such issuers, and/or have a position or holding, or other material interest, or effect transactions, in such securities or options thereon, or other investments related thereto. In addition, it may make markets in the securities mentioned in the material presented in this report. CS may have, within the last three years, served as manager or co-manager of a public offering of securities for, or currently may make a primary market in issues of, any or all of the entities mentioned in this report or may be providing, or have provided within the previous 12 months, significant advice or investment services in relation to the investment concerned or a related investment. Additional information is, subject to duties of confidentiality, available on request. Some investments referred to in this report will be offered solely by a single entity and in the case of some investments solely by CS, or an associate of CS or CS may be the only market maker in such investments. Past performance should not be taken as an indication or guarantee of future performance, and no representation or warranty, express or implied, is made regarding future performance. Information, opinions and estimates contained in this report reflect a judgment at its original date of publication by CS and are subject to change without notice. The price, value of and income from any of the securities or financial instruments mentioned in this report can fall as well as rise. The value of securities and financial instruments is subject to exchange rate fluctuation that may have a positive or adverse effect on the price or income of such securities or financial instruments. Investors in securities such as ADR's, the values of which are influenced by currency volatility, effectively assume this risk. Structured securities are complex instruments, typically involve a high degree of risk and are intended for sale only to sophisticated investors who are capable of understanding and assuming the risks involved. The market value of any structured security may be affected by changes in economic, financial and political factors (including, but not limited to, spot and forward interest and exchange rates), time to maturity, market conditions and volatility, and the credit quality of any issuer or reference issuer. Any investor interested in purchasing a structured product should conduct their own investigation and analysis of the product and consult with their own professional advisers as to the risks involved in making such a purchase. Some investments discussed in this report may have a high level of volatility. High volatility investments may experience sudden and large falls in their value causing losses when that investment is realised. Those losses may equal your original investment. Indeed, in the case of some investments the potential losses may exceed the amount of initial investment and, in such circumstances, you may be required to pay more money to support those losses. Income yields from investments may fluctuate and, in consequence, initial capital paid to make the investment may be used as part of that income yield. Some investments may not be readily realisable and it may be difficult to sell or realise those investments, similarly it may prove difficult for you to obtain reliable information about the value, or risks, to which such an investment is exposed. This report may provide the addresses of, or contain hyperlinks to, websites. Except to the extent to which the report refers to website material of CS, CS has not reviewed any such site and takes no responsibility for the content contained therein. Such address or hyperlink (including addresses or hyperlinks to CS's own website material) is provided solely for your convenience and information and the content of any such website does not in any way form part of this document. Accessing such website or following such link through this report or CS's website shall be at your own risk. This report is issued and distributed in Europe (except Switzerland) by Credit Suisse Securities (Europe) Limited, One Cabot Square, London E14 4QJ, England, which is authorised by the Prudential Regulation Authority ("PRA") and regulated by the Financial Conduct Authority ("FCA") and the PRA. This report is being distributed in Germany by Credit Suisse Securities (Europe) Limited Niederlassung Frankfurt am Main regulated by the Bundesanstalt fuer Finanzdienstleistungsaufsicht ("BaFin"). This report is being distributed in the United States and Canada by Credit Suisse Securities (USA) LLC; in Switzerland by Credit Suisse AG; in Brazil by Banco de Investimentos Credit Suisse (Brasil) S.A or its affiliates; in Mexico by Banco Credit Suisse (México), S.A. (transactions related to the securities mentioned in this report will only be effected in compliance with applicable regulation); in Japan by Credit Suisse Securities (Japan) Limited, Financial Instruments Firm, Director-General of Kanto Local Finance Bureau (*Kinsho*) No. 66, a member of Japan Securities Dealers Association, The Financial Futures Association of Japan, Japan Investment Advisers Association, Type II Financial Instruments Firms Association; elsewhere in Asia/ Pacific by whichever of the following is the appropriately authorised entity in the relevant jurisdiction: Credit Suisse (Hong Kong) Limited, Credit Suisse Equities (Australia) Limited, Credit Suisse Securities (Thailand) Limited, having registered address at 990 Abdulrahim Place, 27 Floor, Unit 2701, Rama IV Road, Silom, Bangrak, Bangkok 10500, Thailand, Tel. +66 2614 6000, Credit Suisse Securities (Malaysia) Sdn Bhd, Credit Suisse AG, Singapore Branch, Credit Suisse Securities (India) Private Limited regulated by the Securities and Exchange Board of India (registration Nos. INB230970637; INF230970637; INB010970631; INF010970631), having registered address at 9th Floor, Ceejay House, Dr.A.B. Road, Worli, Mumbai - 18, India, T- +91-22 6777 3777, Credit Suisse Securities (Europe) Limited, Seoul Branch, Credit Suisse AG, Taipei Securities Branch, PT Credit Suisse Securities Indonesia, Credit Suisse Securities (Philippines) Inc., and elsewhere in the world by the relevant authorised affiliate of the above. Research on Taiwanese securities produced by Credit Suisse AG, Taipei Securities Branch has been prepared by a registered Senior Business Person. Research provided to residents of Malaysia is authorised by the Head of Research for Credit Suisse Securities (Malaysia) Sdn Bhd, to whom they should direct any queries on +603 2723 2020. This report has been prepared and issued for distribution in Singapore to institutional investors, accredited investors and expert investors (each as defined under the Financial Advisers Regulations) only, and is also distributed by Credit Suisse AG, Singapore branch to overseas investors (as defined under the Financial Advisers Regulations). By virtue of your status as an institutional investor, accredited investor, expert investor or overseas investor, Credit Suisse AG, Singapore branch is exempted from complying with certain compliance requirements under the Financial Advisers Act, Chapter 110 of Singapore (the "FAA"), the Financial Advisers Regulations and the relevant Notices and Guidelines issued thereunder, in respect of any financial advisory service which Credit Suisse AG, Singapore branch may provide to you. This research may not conform to Canadian disclosure requirements. In jurisdictions where CS is not already registered or licensed to trade in securities, transactions will only be effected in accordance with applicable securities legislation, which will vary from jurisdiction to jurisdiction and may require that the trade be made in accordance with applicable exemptions from registration or licensing requirements. Non-U.S. customers wishing to effect a transaction should contact a CS entity in their local jurisdiction unless governing law permits otherwise. U.S. customers wishing to effect a transaction should do so only by contacting a representative at Credit Suisse Securities (USA) LLC in the U.S. Please note that this research was originally prepared and issued by CS for distribution to their market professional and institutional investor customers. Recipients who are not market professional or institutional investor customers of CS should seek the advice of their independent financial advisor prior to taking any investment decision based on this report or for any necessary explanation of its contents. This research may relate to investments or services of a person outside of the UK or to other matters which are not authorised by the PRA and regulated by the FCA and the PRA or in respect of which the protections of the PRA and FCA for private customers and/or the UK compensation scheme may not be available, and further details as to where this may be the case are available upon request in respect of this report. CS may provide various services to US municipal entities or obligated persons ("municipalities"), including suggesting individual transactions or trades and entering into such transactions. Any services CS provides to municipalities are not viewed as "advice" within the meaning of Section 975 of the Dodd-Frank Wall Street Reform and Consumer Protection Act. CS is providing any such services and related information solely on an arm's length basis and not as an advisor or fiduciary to the municipality. In connection with the provision of the any such services, there is no agreement, direct or indirect, between any municipality (including the officials, management, employees or agents thereof) and CS for CS to provide advice to the municipality. Municipalities should consult with their financial, accounting and legal advisors regarding any such services provided by CS. In addition, CS is not acting for direct or indirect compensation to solicit the municipality on behalf of an unaffiliated broker, dealer, municipal securities dealer, municipal advisor, or investment adviser for the purpose of obtaining or retaining an engagement by the municipality for or in connection with Municipal Financial Products, the issuance of municipal securities, or of an investment adviser to provide investment advisory services to or on behalf of the municipality. If this report is being distributed by a financial institution other than Credit Suisse AG, or its affiliates, that financial institution is solely responsible for distribution. Clients of that institution should contact that institution to effect a transaction in the securities mentioned in this report or require further information. This report does not constitute investment advice by Credit Suisse to the clients of the distributing financial institution, and neither Credit Suisse AG, its affiliates, and their respective officers, directors and employees accept any liability whatsoever for any direct or consequential loss arising from their use of this report or its content. Principal is not guaranteed. Commission is the commission rate or the amount agreed with a customer when setting up an account or at any time after that.

Investment principal on bonds can be eroded depending on sale price or market price. In addition, there are bonds on which investment principal can be eroded due to changes in redemption amounts. Care is required when investing in such instruments.

When you purchase non-listed Japanese fixed income securities (Japanese government bonds, Japanese municipal bonds, Japanese government guaranteed bonds, Japanese corporate bonds) from CS as a seller, you will be requested to pay the purchase price only.