Chimerix

CMRX : NASDAQ : US$18.80

BUY

Target: US$34.00

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COMPANY STATISTICS:

Forecast Return:	81%
Shares Out (M):	26.5
Market Cap (M):	US$498.2
52-week Range:	US$12.96 - 27.00

EARNINGS SUMMARY:

FYE Dec		2013E	2014E	2015E
Revenue:		4.7	2.6	80.0
EPS:		(3.55)	(2.14)	0.76
Revenue:	Q1	1.8A	0.6	-
	Q2	0.8A	0.6	-
	Q3	0.9A	0.6	-
	Q4	1.2	0.6	-
Total		4.7	2.6	80.0
EPS:	Q1	(22.58)A	(0.50)	-
	Q2	(0.91)A	(0.52)	-
	Q3	(0.26)A	(0.55)	-
	Q4	(0.48)	(0.57)	-
Total		(3.55)	(2.14)	0.76

SHARE PRICE PERFORMANCE:

Source: Interactive Data Corporation

COMPANY DESCRIPTION:

Chimerix focuses on novel, oral antiviral therapeutics in areas of high unmet need. Its proprietary lipid technology has given rise to CMX001, which is in Phase 3 and could become the first broad-spectrum antiviral against double-stranded DNA (dsDNA) viruses, and CMX157, a Phase 1 candidate for the treatment of HIV, licensed to Merck.

All amounts in US$ unless otherwisenoted.

Life Sciences -- Biotechnology

CHANGING PARADIGMS FOR POST-TRANSPLANT INFECTION RISK; INITIATING WITH BUY, $34 TARGET

Investment recommendation

Initiating coverage with BUY, $34 target: We think CMRX's brincidofovir could be a game-changer for the management of post-transplant viral infections. We think brincidofovir could greatly improve post-transplant care for patients at risk for CMV and other double-stranded DNA viral infections like AdV and BKV. We think the Ph3 SUPPRESS trial for CMV prevention has a high chance of success, supporting US and EU approval. Further, given the drug's therapeutic profile, including lack of bone marrow suppression and kidney toxicity as well as activity against AdV and BKV, we think brincidofovir could become standard of care for bone marrow and select solid organ transplants.

Investment highlights

- **We think Phase 3 brincidofovir could become the gold standard treatment for CMV risk post-bone marrow transplant.** Brincidofovir (brin) is a more potent and likely safer form of the current second-line antiviral cidofovir. Not only could brin become the preferred CMV prevention therapy due to its lack of bone marrow suppression and kidney toxicity, but we think it could move the BMT CMV Tx paradigm toward prophylaxis vs. preemptive Tx. We also think brin will prove to have a very manageable side-effect profile.
- **Brin could also see major use in solid organ transplants due to its activity against AdV, BKV.** Brin has shown potent activity against all dsDNA viruses, including AdV, particularly dangerous in pediatric patients, and BKV, which can damage kidney transplants. There could be broad use of brin in select solid organ patient populations.
- **We think the ongoing SUPPRESS trial has a high chance of success and brincidofovir has the potential for $1,179M in peak sales.** The Phase 2 CMV trial showed ~75% reduction in disease rates vs. PBO. The ongoing Ph3 SUPPRESS trial only needs to show a 50% reduction to be successful and support conditional approval. We estimate peak US brin sales of $610M in HSCT and $569M in SOT.

Figure 1: CMRX upcoming catalysts

Expected date	Drug/Program	Item	Impact
Q3/14	CMX001 in CMV	Complete enrollment for SUPPRESS	+
H1/15	CMX001 in CMV	Ph3 data from SUPPRESS	+++
H1/15	CMX157	MRK to start Ph2 study, CMRX receives milestone	++
H2/15	CMX001 in CMV	NDA submission	++
H1/16	CMX001 in CMV	Approval and launch	+++

Source: Company reports and Canaccord Genuity estimates

Figure 2: CMRX pipeline

Drug/ Program	Disease	Licensing/ Partnership	Preclinical	Phase 1	Phase 2	Phase 3	Post-Marketing
CMX001 (prevention in HSCT, SURPPRESS)	SCD	Wholly owned					
CMX001 (pre-emptive therapy in HSCT Study 202)	AdV	Wholly owned					
CMX001	Smallpox under Animal Efficacy Rule	Wholly owned (ongoing dev with BARDA)					
CMX157	HIV	Out-licensed to Merck					
Chimerix Chemical Library	Influenza, antifungals, CMV/BKC	Wholly owned					

Source: Company website

INVESTMENT THESIS

We think Chimerix's brincidofovir (f.k.a. CMX001) is a very promising new potential drug for the prevention of cytomegalovirus (CMV) and adenovirus (AdV) disease in transplant recipients. Brincidofovir is a liposomally conjugated version of the currently approved antiviral agent cidofovir. The drug has improved cellular uptake and safer clearance, increasing overall potency and safety. CMV and AdV are two of the most common and problematic opportunistic viral infections in the post-transplant setting. Both viral infections often cause significant mortality and morbidity. We think brincidofovir is a broad-spectrum antiviral with what we think is an improved side effect and safety profile compared with available treatment, and the potential for improved efficacy.

Brincidofovir has particular potential as it can simultaneously treat a range of serious opportunistic double-stranded DNA (dsDNA) viral infections that often occur together post-transplant. CMV and AdV are only two of a number of dsDNA viral infection (including BKV, HSV-2 and HHV-6) which can contribute to mortality, morbidity and poor clinical outcomes. Due to the immunocompromised and/or immunosuppressed nature of post-transplant patients, they have often have overlapping dsDNA infections. Unlike most current antivirals such as acyclovir and ganciclovir, brincidofovir has the potential to treat the entire family of dsDNA viruses.

Current drugs for the prevention or preemptive treatment of CMV and AdV have significant side effects and/or inadequate anti-viral potency. The most common drugs for the preemptive treatment of CMV in BMT and prophylaxis in solid organ transplant are ganciclovir and valganciclovir, both of which cause immunosuppression and nephrotoxicity. Immunosuppression can damage a bone marrow graft, causing graft loss or a life-threatening side effect called graft-versus-host disease. Cidofovir is considered a more potent anti-CMV agent, but is associated with severe nephrotoxicity. Neither of these agents has a profile that allows for prophylactic treatment of BMT patients, only preemptive treatment, which broadly considered less effective. Oral valganciclovir is often used for prophylaxis in most solid organ transplant patients, but not kidney transplant patients. Cidofovir is generally used only as second-line treatment in post-transplant viremia due to its significant nephrotoxicity.

We think CMX001's Phase 2 data generated to date, especially in CMV, is highly supportive of clinical benefit and Phase 3 success. We think CMX001's data to date shows excellent antiviral activity across a spectrum of double-stranded DNA viral infections, particularly CMV, AdV and smallpox. Phase 2 CMV prevention data showed a statistically significant reduction of almost 75% on incidence of CMV viremia or disease versus placebo, with no immune suppression or nephrotoxicity. Phase 2 AdV prevention study also showed lower rates of AdV viremia and disease versus placebo across multiple measures. Although data did not reach statistical significance, we believe data statistics was confounded by quantitative limitations of the assay. Further, a compassionate use program for up to 800 patients – consisting of an emergency IND (EIND) and open-label study 350 to treat dsDNA viral infections in patients with no other treatment options – has created a large set of positive efficacy and safety data. This extensive data serves as proof of principle for the use of CMX for the treatment of multiple dsDNA viruses.

We think post-BMT CMV represents the fastest, most cost-effective path to market, and see the SUPPRESS trial as well designed with a high probability of success, supporting FDA

approval. While brincidofovir has shown what we see as compelling efficacy in Phase 2 for AdV and signals of efficacy against BK nephropathy, we think the most straightforward development path with the highest chance of clinical success is approval for prevention of CMV disease. Chimerix intends to pursue Subpart E conditional approval with CMV viremia as the surrogate endpoint, and has FDA buy-in for this pivotal trial design (the recently initiated SUPPRESS trial). Chimerix will then have a post-approval commitment for an outcomes study looking at rates of CMV disease and survival. We think SUPPRESS is well powered (>87% powered to show a 50% reduction rate in CMV viremia or disease) assuming a 30% viremia rate in the placebo group. This threshold efficacy for Phase 3 success is well below the efficacy rate seen in Phase 2, and the trial design are similar enough that we think the Phase 2 data is highly supportive of SUPPRESS.

We think SUPPRESS data will support CMX001 as the dsDNA treatment of choice in the post stem-cell transplant setting, as well as the pediatric and kidney transplants, resulting in peak potential sales of $1,179M in the US. Based on superior safety as well as efficacy that may prove to be better than standard of care in a variety of metrics, we think brincidofovir may become the new standard of care for BMT patients. We think it could potentially become not just the preferred therapy for CMV prevention, but also change the treatment paradigm in BMT from preemptive therapy to prophylactic treatment. Moving standard of care to prophylactic treatment should further improve primary, CMV-related outcomes, as well as secondary outcomes of general morbidity, survival and graft success. Expanded use of prophylactic treatment will also grow the potential market. We also think brincidofovir could become standard of care for solid organ transplant in pediatric patients due to its benefits in prevention of AdV disease (even if this is not a formally labeled indication) as well as standard of care in kidney transplants (due to lack of nephrotoxicity as well as activity against BK nephropathy). We think brincidofovir is far ahead of competitors in development and has the potential for peak sales of $1,179M in the US.

INVESTMENT RISKS

Clinical risk – Chimerix's Phase 3 SUPPRESS trial may not be successful. While we view the SUPPRESS trial as well designed and powered for success based on the Phase 2 data, there is inherent risk to any clinical trial. For instance, if the actual placebo viremia rate varies significantly from the assumed 30%, it could adversely impact trial statistics. Other unpredictable "real-world" factors such as patient demographic and infectious organism profile may adversely impact trial outcome.

Clinical risk – the SUPPRESS trial and other clinical may show brincidofovir to have an unacceptable safety and/or tolerability profile. While brincidofovir has not shown the immunosuppression and nephrotoxicity that is common with other CMV and AdV therapies, it has its own unique side-effect profile. There has been a significant degree of diarrhea seen with brincidofovir, although it is universally reversibly and can be managed with transient dose reduction. However, should the diarrhea in SUPPRESS significantly exceed that seen in the Phase 2, it could threaten chance of regulatory and commercial success.

Clinical risk – Chimerix may fail to generate additional positive supportive data for brincidofovir in AdV and BK. We believe that a significant portion of the drug's commercial potential will come from Phase 2 data supportive of the drug's activity against AdV and BK along with CMV. Should Chimerix be unable to generate either Phase 2 or Phase 3 data

that supports this, brincidofovir's ultimate commercial potential could be adversely impacted.

Regulatory risk – FDA may change its mind on the appropriateness of conditional approval on a surrogate endpoint for brincidofovir. Chimerix plans to file for conditional approval for brincidofovir using viremia as a surrogate endpoint. While we believe FDA finds the design of SUPPRESS trial acceptable for conditional approval, the agency reserves the right the change its mind and decide at a later date that the SUPPRESS viremia data is inadequate to support even conditional approval.

Clinical/regulatory risk – Chimerix may not be successful in meeting the post-approval data requirements required as part of a potential conditional approval. Should SUPPRESS be successful and FDA confer conditional approval on brincidofovir, Chimerix would still obligated to produce positive post BMT CMV disease outcomes data from an acceptable post-approval trial. Should this trial be unsuccessful or produce equivocal data, FDA reserved the right to rescind conditional approval, pulling brincidofovir off the market.

Commercial risk – Chimerix faces competition from cheap, generic well-established therapies as well as potential new therapies. Chimerix's operating results will suffer if they fail to successfully compete with the other biotech and pharma companies (Vical/Astellas, Merck, and Viropharma) that are also creating drugs for CMV and AdV. Currently, the only approved antiviral treatment for CMV in hematopoietic stem cell transplant (HSCT) patients is Cytovene (ganciclovir), and four other antivirals are frequently used. Ganciclovir, foscarnet, and cidofovir are currently generically available, and Valcyte will be generic soon. If competitors succeed in developing, acquiring or licensing drug products that are more effective and/or less costly than CMX001, the availability of competitors' products could limit the demand and could affect the price for CMX001 and other product candidates developed by Chimerix.

Commercial risk – Chimerix plans to hire its own small, specialized sales force. Chimerix currently does not have an organization for sales, marketing, and distribution of pharmaceutical products; the cost of establishing and maintaining such an organization may exceed the cost-effectiveness doing so. Should CMX001 get approved, Chimerix must build its sales, marketing, managerial, and other non-technical capabilities or make arrangements with third parties to perform these services. If Chimerix is unable to build its own sales force or negotiate a strategic partnership for the commercialization of CMX001 in the US, it may be forced to delay potential commercialization of the drug, reduce the scope of sales or marketing in the US, or undertake commercialization activities for CMX001 at the company's expense, resulting in decreased revenue as well as a need for more capital.

Financing risk – Chimerix has sufficient cash to reach SUPPRESS data but not enough to secure final US approval of the drug. Chimerix has stated it has at least enough cash to operate through H2/15 when the SUPPRESS data is due, at which point we think the company will likely have 2-3 quarters of operating cash remaining. This amount will not be able to take the company through to brincidofovir approval even if it expedited. We think Chimerix may consider an equity issue, either after SUPPRESS data or approval, to secure operating expenses as well as funds for the commercial launch of brincidofovir for CMV prevention in the post-BMT setting.

VALUATION

We have built our valuation of Chimerix using a probability-weighted NPV model of peak sales.

Potential upside to valuation

We see the following as potential drivers of upside to our model:

- **Better-than-expected data.** Should the SUPPRESS trial produce even stronger CMV prevention than in the Phase 2 trial (substantially greater than 75% reduction), it would suggest superior potency to current standard of care. If data is particularly strong across primary and secondary endpoints, Chimerix believes it could receive full approval for BMT, without an obligation for a post-approval efficacy trial.
- **Data showing lower rates of late-onset CMV.** Currently, Chimerix anticipates running a post-approval trial in solid organ transplants for CMV prophylaxis. Current prophylaxis regimens in solid organ transplants are characterized by a meaningful rate of late-onset CMV that occurs after the 3-6 month period of prophylaxis. Should brincidofovir prove to reduce rates of late-onset CMV compared to SOC, it could increase the drug's market share in the solid organ transplant market, driving up peak sales potential.
- **Lower-than-expected rates of GI side effects.** Clinical data has shown brincidofovir to have meaningful rates of moderate diarrhea that reduce the overall level of tolerability of the treatment. We have factored in a high diarrhea rate into our market uptake and peak share assumptions. Should the drug prove to have lower rates of diarrhea, peak market could be higher, driving additional value.

Potential downside to valuation

As with all companies in commercial and clinical development, there always exists the risk of failed or in conclusive clinical trials, slower-than-expected commercial launches, or lower-than-expected peak sales, which could lead to downward pressure on the stock. For more detailed risks, see our "Investment Risks" section.

Figure 3: Chimerix valuation

Product Development

Drug name	Indication	Status	Launch	Years to Launch	Years to Launch plus 7	Success	Sales (US$m)	Probability weighted Peak Sales (US$m)	Royalty	Profitability	Probability weighted Peak Profit (US$m)	Discount Factor	NPV (US$)
CMX001	Prevention of CMV infection in HSCT	Phase 3	2017	3	10	65%	609.5	396.2	100%	90%	356.56	9.31	21.74
CMX001	Prevention of CMV infection in SOT	Phase 3	2019	5	12	50%	716.1	358.1	100%	90%	322.27	14.55	12.57
										Total			**34.31**

Source: Company reports and Canaccord Genuity estimates

REVENUE MODEL AND FINANCIALS

Our forecast financial model is built on the assumption that CMX001 will launch in the US in 2017 for use in prevention of CMV infection in hematopoietic stem cell transplant (HSCT) and potential label extension for use in solid organ transplant (SOT) in 2019. Our CMX001 market model in HSCT assumes peak CMX001 market share of 56% in US HSCT patients at high risk of CMV infection and 22% in US HSCT patients at low risk of CMV infection. We assume peak sales will be reached in 2025, seven years from launch.

We assume that CMX001 and potential partner, if any, will price one dose of CMX001 around $1,875 in the US. We assume two doses will be used for each week of treatment for over 14 weeks totaling 28 doses per course, or $45,000. We assume market research would support an even higher pricing based superior phamacoeconomics and safety profile, but are currently modeling with a much more conservative price.

We also modeled use of CMX001 for prevention of CMV disease in solid organ transplant (SOT). Our market model in SOT assumes peak CMX001 market share of 79% in US SOT patients at high risk of CMV infection, 66% in US SOT patients at low risk of CMV infection, 88% in US pediatric SOT patients at high risk of CMV infection, 66% in US pediatric SOT patients at low risk of CMV infection. We note the uptake in the kidney transplant patients will be dependent upon BK activity data, and the market penetration in peds SOT will be largely based on AdV activity data. We assume peak sales will be reached in 2026, seven years from launch.

Overall, we forecast peak sales for CMX001 in 2024 of ~$1,179M, of which $610M came from use in HSCT and $569M from use in SOT. We have not modeled potential revenue streams from EU or ROW, which could increase the peak sales figure significantly.

CMRX reported current asset of $116M on September 30, 2013. We think CMRX has sufficient cash to reach SUPPRESS data but not enough to secure final US approval of the drug. CMRX has stated it has enough cash to operate through H2/15 when the SUPPRESS data is due, at which point we think the company will likely have 2-3 quarters of operating cash remaining. This amount will not be able to take the company through to CMX001 approval even if it expedited. We think CMRX may consider an equity issue either after SUPPRESS data or approval to secure operating expenses as well as funds for the commercial launch of CMX001 for CMV prevention in US HSCT patients.

Figure 4: CMX001 revenue projections

		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
US CMX market model in HSCT														
US population	0.7%	318.3	320.5	322.8	325.1	327.3	329.6	331.9	334.2	336.6	338.9	341.3	343.7	346.1
HSCT procedures		24,349	25,255	26,194	27,169	28,180	29,228	30,316	31,444	32,614	33,828	35,086	36,392	37,746
Incidence	3.0%	0.000076	0.000079	0.000081	0.000084	0.000086	0.000089	0.000091	0.000094	0.000097	0.000100	0.000103	0.000106	0.000109
High risk HSCT patients		12,047	12,451	12,870	13,302	13,748	14,210	14,687	15,180	15,690	16,217	16,762	17,324	17,906
% of all HSCT patients	-0.35%	49.48%	49.30%	49.13%	48.96%	48.79%	48.62%	48.45%	48.28%	48.11%	47.94%	47.77%	47.60%	47.44%
High risk HSCT patients on prophylaxis					1,330	4,125	5,684	7,344	9,108	10,983	12,974	15,085	15,592	16,116
					10.0%	30.0%	40.0%	50.0%	60.0%	70.0%	80.0%	90.0%	90.0%	90.0%
CMX001 market share					100.00%	100.00%	95.00%	85.00%	75.00%	65.00%	55.00%	50.00%	50.00%	50.00%
Other prophylaxis market share					0.00%	0.00%	5.00%	15.00%	25.00%	35.00%	45.00%	50.00%	50.00%	50.00%
High risk HSCT patients on CMX001 prophylaxis					1,330	4,125	5,400	6,242	6,831	7,139	7,135	7,543	7,796	8,058
CMX001 prophylaxis penetration in high risk HSCT pts					10.0%	30.0%	38.0%	42.5%	45.0%	45.5%	44.0%	45.0%	45.0%	45.0%
High risk HSCT patients not on prophylaxis					11,971.51	9,623.84	8,526.01	7,343.59	6,072.15	4,707.04	3,243.40	1,676.16	1,732.44	1,790.62
					90.00%	70.00%	60.00%	50.00%	40.00%	30.00%	20.00%	10.00%	10.00%	10.00%
% with viremia		70.00%	70.00%	70.00%	70.00%	70.00%	70.00%	70.00%	70.00%	70.00%	70.00%	70.00%	70.00%	70.00%
High risk pts - first line treatment														
CMX001 market share					3.00%	6.00%	9.00%	12.00%	15.00%	18.00%	20.00%	20.00%	20.00%	20.00%
Other treatment market share					97.00%	94.00%	91.00%	88.00%	85.00%	82.00%	80.00%	80.00%	80.00%	80.00%
High risk pts - second line treatment														
% failing first line treatment	1.00%	25.76%	26.02%	26.28%	26.54%	26.80%	27.07%	27.34%	27.62%	27.89%	28.17%	28.45%	28.74%	29.02%
High risk HSCT patients on CMX001 treatment					2,475	2,210	2,153	2,022	1,811	1,512	1,094	568	591	614
CMX001 Tx penetration in high risk HSCT pts					18.6%	16.1%	15.1%	13.8%	11.9%	9.6%	6.7%	3.4%	3.4%	3.4%
High risk HSCT patients treated w ith CMX001					3,805	6,334	7,553	8,264	8,643	8,651	8,229	8,111	8,387	8,672
CMX001 blended penetration in high risk HSCT patients					28.6%	46.1%	53.1%	56.3%	56.9%	55.1%	50.7%	48.4%	48.4%	48.4%
Low risk HSCT patients		12,047	12,451	12,870	13,302	13,748	14,210	14,687	15,180	15,690	16,217	16,762	17,324	17,906
% of all HSCT patients	-0.35%	49.48%	49.30%	49.13%	48.96%	48.79%	48.62%	48.45%	48.28%	48.11%	47.94%	47.77%	47.60%	47.44%
Low risk HSCT patients on prophylaxis					266	550	853	1,175	1,518	1,883	2,270	2,514	2,599	2,686
					2.0%	4.0%	6.0%	8.0%	10.0%	12.0%	14.0%	15.0%	15.0%	15.0%
CMX001 market share					100.00%	100.00%	90.00%	80.00%	70.00%	60.00%	50.00%	50.00%	50.00%	50.00%
Other prophylaxis market share					0.00%	0.00%	10.00%	20.00%	30.00%	40.00%	50.00%	50.00%	50.00%	50.00%
Low risk HSCT patients on CMX001 prophylaxis					266	550	767	940	1,063	1,130	1,135	1,257	1,299	1,343
CMX001 prophylaxis penetration in low risk HSCT pts					2.0%	4.0%	5.4%	6.4%	7.0%	7.2%	7.0%	7.5%	7.5%	7.5%
Low risk HSCT patients not on prophylaxis					13,035.65	13,198.41	13,357.41	13,512.21	13,662.34	13,807.31	13,946.62	14,247.33	14,725.75	15,220.24
					98.00%	96.00%	94.00%	92.00%	90.00%	88.00%	86.00%	85.00%	85.00%	85.00%
% with viremia	-1.00%	38.81%	38.42%	38.04%	37.66%	37.28%	36.91%	36.54%	36.18%	35.81%	35.46%	35.10%	34.75%	34.40%
Low risk pts - first line treatment														
CMX001 market share					1.00%	4.00%	7.00%	10.00%	13.00%	16.00%	18.00%	20.00%	20.00%	20.00%
Other treatment market share					99.00%	96.00%	93.00%	90.00%	87.00%	84.00%	82.00%	80.00%	80.00%	80.00%
Low risk pts - second line treatment														
% failing first line treatment	1.00%	25.76%	26.02%	26.28%	26.54%	26.80%	27.07%	27.34%	27.62%	27.89%	28.17%	28.45%	28.74%	29.02%
Low risk HSCT patients on CMX001 treatment					1,352	1,516	1,680	1,844	2,007	2,170	2,283	2,423	2,494	2,567
CMX001 Tx penetration in low risk HSCT pts					10.2%	11.0%	11.8%	12.6%	13.2%	13.8%	14.1%	14.5%	14.4%	14.3%
Low risk HSCT patients treated w ith CMX001					1,618	2,066	2,447	2,784	3,070	3,300	3,418	3,680	3,793	3,910
CMX001 blended penetration in low risk HSCT patients					12.2%	15.0%	17.2%	19.0%	20.2%	21.0%	21.1%	22.0%	21.9%	21.8%
CMX001 penetration in US HSCT patients					20.0%	29.8%	34.2%	36.4%	37.2%	36.6%	34.4%	33.6%	33.5%	33.3%
Total US HSCT pts treated w ith CMX001					5,423	8,400	10,000	11,048	11,713	11,951	11,647	11,791	12,180	12,582
Gross cost	2.0%				45,000.00	45,900.00	46,818.00	47,754.36	48,709.45	49,683.64	50,677.31	51,690.86	52,724.67	53,779.17
Net cost	10.0%				40,500.00	41,310.00	42,136.20	42,978.92	43,838.50	44,715.27	45,609.58	46,521.77	47,452.20	48,401.25
CMX001 US Revenue					244.05	385.56	468.17	527.60	570.51	593.78	590.26	609.51	642.20	676.66

Source: Company reports and Canaccord Genuity estimates

Figure 4 (continued): CMX001 revenue projections

US CMX market model in SOT													
US population	0.7%	318.3	320.5	322.8	325.1	327.3	329.6	331.9	334.2	336.6	338.9	341.3	343.7	346.1
Kidney transplant procedures		15,940	16,059	16,180	16,301	16,424	16,547	16,671	16,796	16,922	17,049	17,177	17,306	17,436
Incidence	0.1%	0.000050	0.000050	0.000050	0.000050	0.000050	0.000050	0.000050	0.000050	0.000050	0.000050	0.000050	0.000050	0.000050
High risk kidney transplant patients		6,309	6,334	6,360	6,385	6,410	6,436	6,461	6,487	6,513	6,539	6,565	6,591	6,617
% of all kidney transplant patients	-0.35%	39.58%	39.44%	39.30%	39.17%	39.03%	38.89%	38.76%	38.62%	38.49%	38.35%	38.22%	38.08%	37.95%
High risk kidney transplant patients on prophylaxis							4,505	4,717	4,930	5,145	5,362	5,580	5,800	5,955
							70.0%	73.0%	76.0%	79.0%	82.0%	85.0%	88.0%	90.0%
CMX001 market share							5.00%	20.00%	35.00%	50.00%	60.00%	70.00%	80.00%	80.00%
Other prophylaxis market share							95.00%	80.00%	65.00%	50.00%	40.00%	30.00%	20.00%	20.00%
High risk kidney transplant patients on CMX001 prophylaxis							225	943	1,726	2,573	3,217	3,906	4,640	4,764
CMX001 prophylaxis in high risk kidney transplant pts							3.5%	14.6%	26.6%	39.5%	49.2%	59.5%	70.4%	72.0%
High risk kidney patients not on prophylaxis							1,930.71	1,744.55	1,556.88	1,367.69	1,176.96	984.70	790.90	661.70
							30.00%	27.00%	24.00%	21.00%	18.00%	15.00%	12.00%	10.00%
% with viremia	-1.00%	67.92%	67.24%	66.57%	65.90%	65.24%	64.59%	63.95%	63.31%	62.67%	62.05%	61.43%	60.81%	60.20%
High risk kidney transplant pts - first line treatment														
CMX001 market share							5.00%	15.00%	30.00%	45.00%	60.00%	70.00%	80.00%	90.00%
Other treatment market share							95.00%	85.00%	70.00%	55.00%	40.00%	30.00%	20.00%	10.00%
High risk kidney transplant pts - second line treatment														
% failing first line treatment	1.00%	25.76%	26.02%	26.28%	26.54%	26.80%	27.07%	27.34%	27.62%	27.89%	28.17%	28.45%	28.74%	29.02%
High risk kidney transplant pts on CMX001 treatment							400	472	568	625	644	596	523	474
CMX001 Tx in high risk kidney transplant pts							6.2%	7.3%	8.8%	9.6%	9.8%	9.1%	7.9%	7.2%
High risk kidney transplant patients treated w ith CMX001							625	1,416	2,293	3,197	3,861	4,502	5,163	5,238
CMX001 blended penetration in high risk kidney transplant pts							9.7%	21.9%	35.4%	49.1%	59.0%	68.6%	78.3%	79.2%
Low risk kidney transplant patients		9,631	9,725	9,820	9,917	10,013	10,111	10,210	10,309	10,409	10,510	10,612	10,715	10,819
% of all kidney transplant patients	-0.35%	60.42%	60.56%	60.70%	60.83%	60.97%	61.11%	61.24%	61.38%	61.51%	61.65%	61.78%	61.92%	62.05%
Low risk kidney transplant patients on prophylaxis							2,022	2,450	2,887	3,331	3,784	4,245	4,822	5,409
							20.0%	24.0%	28.0%	32.0%	36.0%	40.0%	45.0%	50.0%
CMX001 market share							5.00%	20.00%	40.00%	55.00%	70.00%	80.00%	85.00%	90.00%
Other prophylaxis market share							95.00%	80.00%	60.00%	45.00%	30.00%	20.00%	15.00%	10.00%
Low risk kidney transplant patients on CMX001 prophylaxis							101	490	1,155	1,832	2,649	3,396	4,099	4,868
CMX001 prophylaxis in low risk kidney transplant pts							1.0%	4.8%	11.2%	17.6%	25.2%	32.0%	38.3%	45.0%
Low risk kidney transplant patients not on prophylaxis							8,088.97	7,759.43	7,422.61	7,078.39	6,726.71	6,367.44	5,893.35	5,409.41
							80.00%	76.00%	72.00%	68.00%	64.00%	60.00%	55.00%	50.00%
% with viremia	-1.00%	38.81%	38.42%	38.04%	37.66%	37.28%	36.91%	36.54%	36.18%	35.81%	35.46%	35.10%	34.75%	34.40%
Low risk kidney transplant pts - first line treatment														
CMX001 market share							5.00%	15.00%	30.00%	45.00%	60.00%	70.00%	80.00%	90.00%
Other treatment market share							95.00%	85.00%	70.00%	55.00%	40.00%	30.00%	20.00%	10.00%
Low risk kidney transplant pts - second line treatment														
% failing first line treatment	1.00%	25.76%	26.02%	26.28%	26.54%	26.80%	27.07%	27.34%	27.62%	27.89%	28.17%	28.45%	28.74%	29.02%
Low risk kidney transplant pts on CMX001 treatment							958	1,201	1,547	1,848	2,103	2,200	2,227	2,215
CMX001 Tx in low risk kidney transplant pts							9.5%	11.8%	15.0%	17.8%	20.0%	20.7%	20.8%	20.5%
Low risk kidney transplant patients treated w ith CMX001							1,059	1,691	2,702	3,680	4,751	5,596	6,325	7,083
CMX001 blended penetration in low risk kidney transplant pts							10.5%	16.6%	26.2%	35.4%	45.2%	52.7%	59.0%	65.5%
CMX001 penetration in US kidney transplant patients							10.2%	18.6%	29.7%	40.6%	50.5%	58.8%	66.4%	70.7%
Total US kidney transplant pts treated w ith CMX001							1,684	3,106	4,995	6,977	8,612	10,098	11,488	12,322
US population	0.7%	318.3	320.5	322.8	325.1	327.3	329.6	331.9	334.2	336.6	338.9	341.3	343.7	346.1
Peds SOT procedures		6,376	6,424	6,472	6,521	6,569	6,619	6,668	6,718	6,769	6,820	6,871	6,922	6,974
Incidence	0.1%	0.000020	0.000020	0.000020	0.000020	0.000020	0.000020	0.000020	0.000020	0.000020	0.000020	0.000020	0.000020	0.000020
High risk peds SOT patients		2,524	2,534	2,544	2,554	2,564	2,574	2,585	2,595	2,605	2,615	2,626	2,636	2,647
% of all peds SOT patients	-0.35%	39.58%	39.44%	39.30%	39.17%	39.03%	38.89%	38.76%	38.62%	38.49%	38.35%	38.22%	38.08%	37.95%
High risk peds SOT patients on prophylaxis							1,802	1,887	1,972	2,058	2,145	2,232	2,320	2,382
							70.0%	73.0%	76.0%	79.0%	82.0%	85.0%	88.0%	90.0%
CMX001 market share							5.00%	20.00%	40.00%	55.00%	70.00%	80.00%	85.00%	90.00%
Other prophylaxis market share							95.00%	80.00%	60.00%	45.00%	30.00%	20.00%	15.00%	10.00%
High risk peds SOT patients on CMX001 prophylaxis							90	377	789	1,132	1,501	1,786	1,972	2,144
CMX001 prophylaxis in high risk peds SOT pts							3.5%	14.6%	30.4%	43.5%	57.4%	68.0%	74.8%	81.0%
High risk peds SOT not on prophylaxis							772.28	697.82	622.75	547.07	470.79	393.88	316.36	264.68
							30.00%	27.00%	24.00%	21.00%	18.00%	15.00%	12.00%	10.00%
% with viremia	-1.00%	67.92%	67.24%	66.57%	65.90%	65.24%	64.59%	63.95%	63.31%	62.67%	62.05%	61.43%	60.81%	60.20%
High risk peds SOT pts - first line treatment														
CMX001 market share							5.00%	15.00%	30.00%	45.00%	60.00%	70.00%	80.00%	90.00%
Other treatment market share							95.00%	85.00%	70.00%	55.00%	40.00%	30.00%	20.00%	10.00%
High risk peds SOT pts - second line treatment														
% failing first line treatment	1.00%	25.76%	26.02%	26.28%	26.54%	26.80%	27.07%	27.34%	27.62%	27.89%	28.17%	28.45%	28.74%	29.02%
High risk peds SOT pts on CMX001 treatment							160	189	227	250	258	238	209	190
CMX001 Tx in high risk peds SOT pts							6.2%	7.3%	8.8%	9.6%	9.8%	9.1%	7.9%	7.2%
High risk peds SOT patients treated w ith CMX001							250	566	1,016	1,382	1,759	2,024	2,181	2,331
CMX001 blended penetration in high risk peds SOT pts							9.7%	21.9%	39.2%	53.0%	67.2%	77.1%	82.7%	88.2%
Low risk peds SOT patients		192	194	196	198	200	201	203	205	207	209	211	213	215
% of all peds SOT patients	-0.35%	60.42%	60.56%	60.70%	60.83%	60.97%	61.11%	61.24%	61.38%	61.51%	61.65%	61.78%	61.92%	62.05%
Low risk peds SOT patients on prophylaxis							40	49	57	66	75	84	96	107
							20.0%	24.0%	28.0%	32.0%	36.0%	40.0%	45.0%	50.0%
CMX001 market share							5.00%	20.00%	40.00%	55.00%	70.00%	80.00%	85.00%	90.00%
Other prophylaxis market share							95.00%	80.00%	60.00%	45.00%	30.00%	20.00%	15.00%	10.00%
Low risk peds SOT patients on CMX001 prophylaxis							2	10	23	36	53	67	81	97
CMX001 prophylaxis in low risk peds SOT pts							1.0%	4.8%	11.2%	17.6%	25.2%	32.0%	38.3%	45.0%
Low risk peds SOT patients not on prophylaxis							161.13	154.49	147.71	140.79	133.73	126.52	117.04	107.38
							80.00%	76.00%	72.00%	68.00%	64.00%	60.00%	55.00%	50.00%
% with viremia	-1.00%	38.81%	38.42%	38.04%	37.66%	37.28%	36.91%	36.54%	36.18%	35.81%	35.46%	35.10%	34.75%	34.40%
Low risk peds SOT pts - first line treatment														
CMX001 market share							5.00%	15.00%	30.00%	45.00%	60.00%	70.00%	80.00%	90.00%
Other treatment market share							95.00%	85.00%	70.00%	55.00%	40.00%	30.00%	20.00%	10.00%
Low risk peds SOT pts - second line treatment														
% failing first line treatment	1.00%	25.76%	26.02%	26.28%	26.54%	26.80%	27.07%	27.34%	27.62%	27.89%	28.17%	28.45%	28.74%	29.02%
Low risk peds SOT pts on CMX001 treatment							19	24	31	37	42	44	44	44
CMX001 Tx penetration in low risk peds SOT pts							9.5%	11.8%	15.0%	17.8%	20.0%	20.7%	20.8%	20.5%
Low risk peds SOT patients treated w ith CMX001							21	34	54	73	94	111	126	141
CMX001 blended penetration in low risk peds SOT pts							10.5%	16.6%	26.2%	35.4%	45.2%	52.7%	59.0%	65.5%
CMX001 penetration in US peds SOT patients							4.1%	9.0%	15.9%	21.5%	27.2%	31.1%	33.3%	35.5%
Total US peds SOT pts treated w ith CMX001							271	600	1,070	1,455	1,853	2,135	2,307	2,474
Total US SOT pts (kidney and all peds) treated w ith CMX001							1,955	3,706	6,065	8,332	10,466	12,233	13,795	14,796
% penetration							8.4%	15.9%	25.8%	35.2%	43.8%	50.9%	56.9%	60.6%
Gross cost	2.0%						46,818.00	47,754.36	48,709.45	49,683.64	50,677.31	51,690.86	52,724.67	53,779.17
Net cost	10.0%						42,136.20	42,978.92	43,838.50	44,715.27	45,609.58	46,521.77	47,452.20	48,401.25
CMX001 US Revenue							82.38	159.29	265.87	372.58	477.34	569.10	654.61	716.15

Source: Company reports and Canaccord Genuity estimates

RECOMMENDATION

We believe brincidofovir will become a critical part of CMV disease prevention in the post-transplant setting, and very likely the treatment of choice in price-independent situations. SUPPRESS, Chimerix's Phase 3 trial for brincidofovir, has, in our analysis, a high chance of success based on positive Phase 2 data, similarities in trial design between Phase 2 and 3, and the overall design and powering of the SUPPRESS trial. We think SUPPRESS will yield positive data in late 2015 or early 2016, depending on enrollment rates.

We think Chimerix will also produce supportive data (from SUPPRESS or other trials) showing efficacy against adenovirus disease, particularly problematic in pediatric transplant patients, as well as efficacy data against BK nephropathy, another double-stranded viral infection that can be particularly dangerous for kidney transplant patients.

If SUPPRESS data is what we anticipate, we think brincidofovir will be conditionally approved in the US and possibly the EU in 2017. Chimerix will likely have a Phase 4 post-marketing commitment for a solid organ transplant trial that should serve the simultaneous purpose of supporting a label expansion into solid organ transplant patients.

Brincidofovir could then quickly become standard of care treatment for CMV disease prevention in the bone marrow transplant/stem cell transplant setting. In our analysis, brincidofovir could offer a superior therapeutic profile to current treatment such as ganciclovir and cidofovir due to its lack of bone marrow suppression and kidney toxicity. We also think the drug will become standard of care for pediatric solid organ transplant patients as well as kidney transplant patients of all ages once adenovirus and BK virus data is produced. We think that the diarrhea side effect seen with the drug is very manageable with the side-effect management algorithm that Chimerix has instituted for the SUPRESS trial.

Further, we think brincidofovir will prove to be safe enough that the treatment of post-BMT will move to prophylactic treatment rather than the current paradigm of post-disease, which will both improve patient care as well as expand the market opportunity. All of this leads us to believe that brincidofovir could reach peak sales of $1,179M in the US.

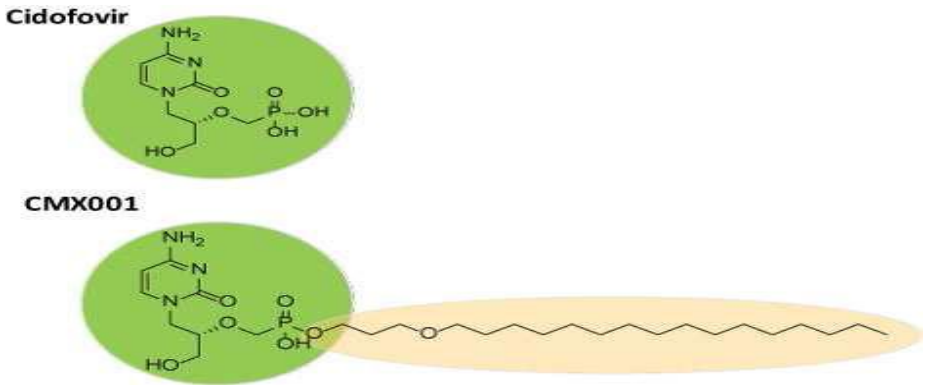
COMPANY OVERVIEW

Chimerix is a biopharmaceutical company that focuses on the discovery, development, and commercialization of novel, oral antiviral therapeutics that can transform patient care in areas of high unmet need. Their proprietary lipid technology has given rise to two clinical-stage compounds, CMX001 and CMX157, both of which have demonstrated the potential for enhanced antiviral activity and safety in orally administered dosing regimens. CMX001 is undergoing a Phase 3 SUPPRESS study for the prevention of cytomegalovirus (CMV) infection in hematopoietic stem cell transplant (HSCT) recipients. CMX001 has the potential to be developed into the first broad-spectrum antiviral against double-stranded DNA (dsDNA) viruses. CMX157 is a Phase 1 product candidate for the treatment of HIV and was licensed to Merck in 2012.

CMX001 IS ACTIVE AGAINST DOUBLE-STRANDED DNA VIRUSES

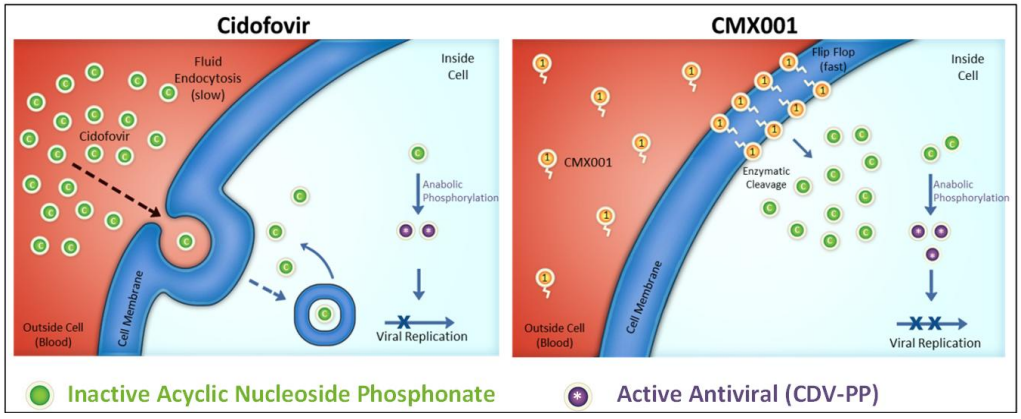
CMX001 is a lipophilic nucleotide analog of a lipid that facilitates transmembrane uptake. This allows intracellular delivery of cidofovir (CDV), thereby lowering the side effects of the drug. Chimerix's proprietary technology modifies a drug molecule so that it mimics a naturally occurring phospholipid metabolite. The lipid mimic can then proceed with the body's natural uptake pathways, giving already existing antiviral compounds higher antiviral bioavailability, tolerability, and activity. It lowers the plasma concentration of CDF and increases the intracellular uptake of the antiviral agent.

Figure 5: Structure of cidofovir and CMX001



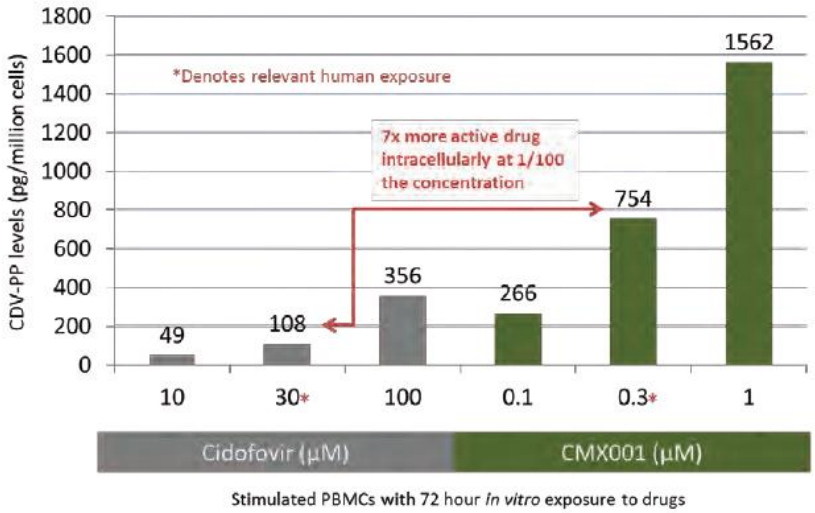
Source: Company website

Figure 6: Intracellular activation and site of action of CMX001 and plasma concentrations vs. cidofovir



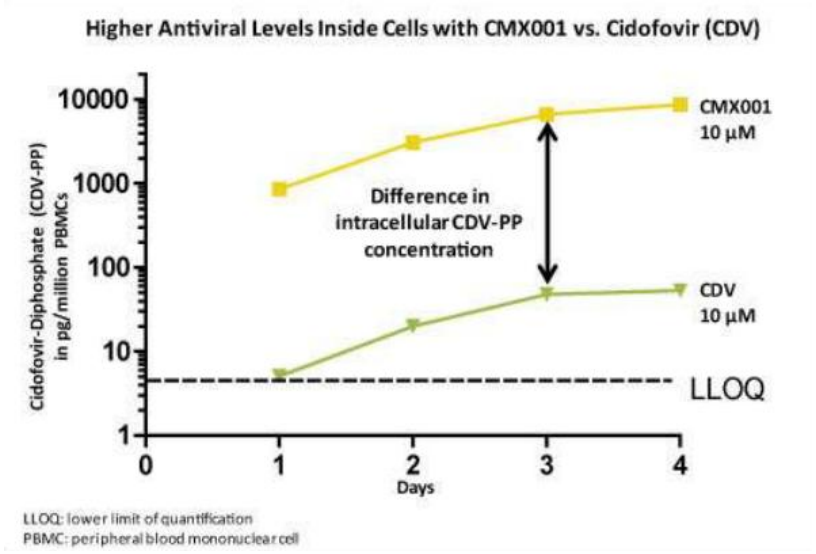
Source: Company presentation

Figure 7: Concentrations of cidofovir diphosphate (µM) in human PBMCs after in vitro incubation with CMX001 or CDV



Source: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM283285.pdf

Figure 8: CMX001 yields higher level of antivirals inside cell



Source: Company website (S-1)

By inhibiting DNA polymerization and thus viral replication, CMX001 reduces the viral burden to the host cell. CMX001 is formed by conjugating a lipid, 3-hexadecyloxy-1-propanol, to the phosphate moiety of CDV. Once the CMX001 is inside the cell, CDV is liberated by phospholipase cleavage of the lipid ester linkage and activated by two successive phosphorylations. The first phosphorylation converts CDV to cidofovir

monophosphate (CDV-P) and the second phosphorylation converts CDV-P to cidofovir diphosphate (CDV-PP). CDV-PP acts as a competitive, alternative inhibitor of the DNA directed DNA polymerases encoded by the herpesvirus, adenovirus and orthopox viruses families of double-stranded DNA virus. CMX001 has potent and broad-spectrum activity against dsDNA viruses.

Figure 9: Activity spectrum of CMX001 and other antiviral against dsDNA viruses

Viral Family	Virus	CMX001	Cidofovir	Ganciclovir*	Foscarnet	Acyclovir	Maribavir	Letermovir
Herpes	Cytomegalovirus (CMV)	0.001	0.4	3.8	50-800	>200	0.31	0.0051
	Epstein-Barr Virus (EBV)	0.03	65.6	0.9	<500	6.2	0.63	>10
	Human Herpesvirus 6A (HHV-6A)	0.003	2.7	5.8	16	10	Inactive	>10
	Human Herpesvirus 8 (HHV-8)	0.02	2.6	8.9	177	>100	Inactive	No data
	Herpes Simplex Virus 1 (HSV-1)	0.01	3.0	0.7	92-95	3.8	Inactive	>10
	Herpes Simplex Virus 2 (HSV-2)	0.02	6.5	2.5	91-96	4.4	Inactive	>10
	Varicella Zoster Virus (VZV)	0.0004	0.5	1.3	39.8	3.6	Inactive	>10
Adenovirus	Adenovirus 7 (AdV7)	0.02	1.3	4.5-33	Inactive (AdV2)	>100	No data	>10 (AdV2)
Polyoma	BK Virus (BKV)	0.13	115	>200	Inactive	>200	No data	No data
	JC Virus (JCV)	0.045	>0.1	No data	Inactive	No data	No data	No data
Papilloma	Human Papillomavirus 11 (HPV-11)	17	716	Inactive	No data	Inactive	No data	No data
Pox	Variola	0.1	27	No data	No data	No data	No data	No data
	Vaccinia	0.8	46	>392	Inactive	>144	No data	No data

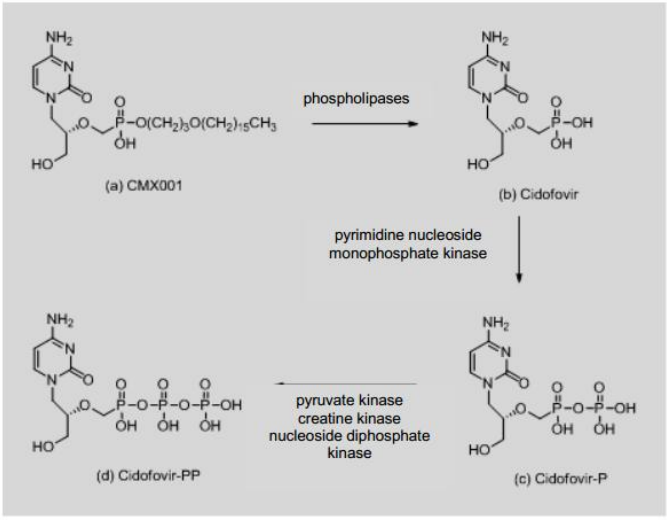
EC_{50} = concentration in µM required to reduce viral replication by 50% *in vitro*.
Data are compiled from multiple sources and include multiple materials and methodologies.
*Valganciclovir is rapidly converted to ganciclovir *in vivo*. Therefore, ganciclovir is the relevant compound for cell activity studies.

Source: Company presentation

CDV is a cytosine analogue and is efficiently incorporated into the nascent chain DNA by viral DNA polymerases. This process can lead to lowering of the overall rate of viral DNA synthesis. The incorporation of one molecule of CDV into a synthetic DNA primer by human CMV DNA polymerases slows the rate of DNA synthesis by 31%. The incorporation of a second CDV molecule halts further DNA elongation. In vivo, various regimens of CDV have failed to produce drug resistant viruses because CDV does not require phosphorylation by viral kinases.

The increased antiviral efficacy associated with CMX001 is directly proportional to higher intracellular levels of CDV-PP. Much less CMX001 must be administered to achieve a physiologically relevant level of intracellular CDV compared with the amount of CDV that had to be used to achieve similar concentrations.

Figure 10: CDV mechanism of action



Source:http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisory Committee/UCM283285.pdf

CMX001 is gaining traction through its compassionate use program that includes an Emergency IND and an open label study through which patients with dsDNA viral infections and no current treatment options are given CMX001. CMX001 received an Emergency IND (EIND) so that 226 patients from over 100 centers worldwide can be treated for herpesviruses (CMV, HSV, EBV, HHV-6), AdV, BKV, and JCV. In "open label study 350," 215 patients from 36 sites in the US are being treated for CMV, AdV, and HSV. Pediatric and renal insufficiency safety and PK data are being collected from more than half of the overall 800+ patients results stored in study database. Exploring the database serves as proof-of-concept data for CMX001 and its efficacy in the treatment of multiple dsDNA viruses.

CYTOMEGALOVIRUS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Background on cytomegalovirus (CMV)

CMV infections continue to be a serious cause of morbidity in solid organ and stem cell transplant recipients. CMV commonly manifests as an opportunistic pathogen in suppressed immune systems. It is a herpesvirus that is spread through direct contact and viral shedding that occurs in body fluids. CMV takes a significant physiological toll on patients with AIDS and other immunodeficiency orders, solid organ and bone marrow transplant patients, those taking chromic immunosuppressive medications, and those with underlying malignancies. CMV is found in all geographic locations and infects 50-80% of adults in the United States (~40% worldwide) as indicated by the presence of antibodies in the population. Primary CMV infections in immunocompetent individuals are usually asymptomatic, which may have contributed to the high prevalence of the virus..

CMV can lead to lethal complications following HSCT and 65% of all patients undergoing HSCT are at risk for CMV. The disease is usually a result of latent virus reactivation and is defined by CMV detection in peripheral blood samples (PCR). In clinical settings, elevations in peripheral white blood cell count, platelet count, or transaminase concentration are all telltale signs of CMV syndrome. In tissue invasive disease, the transplanted allograft is usually involved, although organs such as the lungs or heart may be affected as well. The most common form of the disease is manifested in the gastrointestinal tract.

Mismatched donors and carriers, CMV-seronegative recipients (R-) of organs from seropositive donors (D+), are at the highest risk of developing CMV infection and disease. In the absence of an effective prevention strategy, 80-100% of the D+/R- recipients will contract CMV infection, of which 50-70% will develop CMV disease. R+ recipients are at intermediate risk, and D-/R- recipients present the lowest risk. Other risk factors for CMV-related complications post-HSCT include: age of donor/recipient, nature and intensity of immunosuppression, time since transplantation, and other co-infections.

Exposure to CMV increases with age, therefore pediatric patients are more likely to be CMV seronegative prior to a transplant and transplanted organs from adult donors are more likely to have latent CMV. Thus, pediatric patients are at particularly high risk of CMV-related complications. Lung and small intestine transplant recipients are associated with the highest risk of developing CMV infection while liver and heart recipients have a lower risk. Renal transplant recipients have the lowest risk of infection due to lower burden of latent virus in the renal allograft. In any case, the consequences for any recipient who becomes infected with CMV are severe and should be avoided at all cost.

Structure of CMV

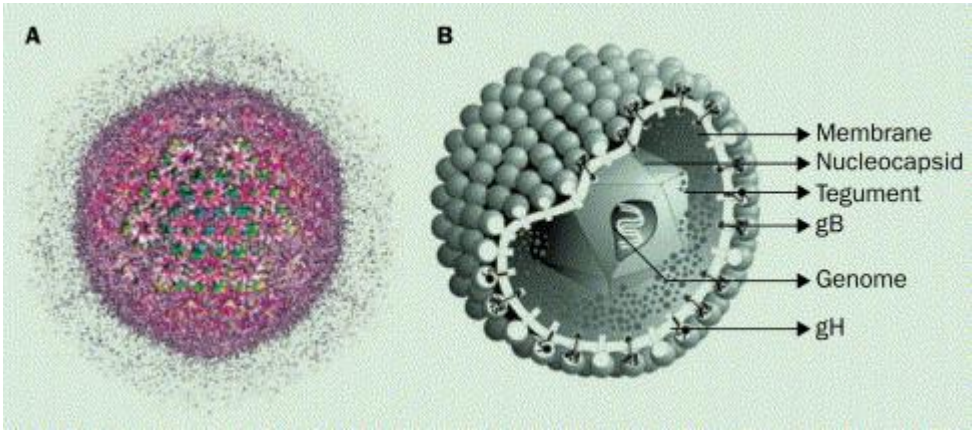
The structure of CMV is typical of the herpes virus family: the 235 kb double-stranded DNA genome is encased by the nucleocapsid to form a core, which is surrounded by the protein rich tegument layer, which is in turn surrounded by the bi-layer lipid envelope.

To gain entry into the cell, glycoproteins on the surface of the lipid envelope fuse with the outer membrane of the cell, after which tegument proteins and the nucleocapsid are released into the cell. Tegument proteins become active upon release into the cell, and

control viral entry, gene expression, and immune evasion, playing a key role in the earliest and last steps of the HCMV replication cycle. Phosphoprotein-65 (pp65) is the most abundant tegument protein and is a key player in the modulating/evading of the host cell immune response during infection.

Several studies suggest that pp65 protects infected cells from being destroyed, and that it may bind to components of the immune system, inhibiting their action. Pp65 has been shown to block MHC-I presentation of early viral proteins, and it may play a role in decreasing expression of MHC-II expression. MHC-I and MHC-II are responsible for lymphocyte recognition and antigen presentation. HCMV surface glycoprotein B (gB) is the major component of the viral envelope, and plays a role in virus attachment, penetration, and cell-to-cell spread. It is a type-1 transmembrane glycoprotein. It is also an important target for humoral and cell immune responses.

Figure 11: Structure of CMV



Source: http://www.sciencedirect.com/science/article/pii/S1473309904012022

Detection and diagnosis

CMV viral loads are now quantified using real-time polymerase chain reaction (RT-PCR). The virus is usually undetectable in the blood from healthy persons even if they were previously exposed to the virus. Immunosuppressed patients may have stable low viral loads, even in the absence of disease. Increasing viral load over time suggests progression of active disease. The reportable range of quantitative PCR for CMV is 1000-100,000 copies of CMV DNA/mL. A negative result (>1000 copies/mL) doesn't rule out the presence of CMV in concentrations below the level of detection of the assay.

Measurement of CMV-specific IgG avidity has also proven to be a powerful tool for distinguishing primary from non-primary CMV infection. IgG avidity is defined as the strength with which the IgG attaches to the antigen. It matures with the length of time following primary infection. Therefore, the IgG produced within the first few months following primary infection shows low avidity, while that produced several months or years later produces a higher avidity. A CMV specific IgG avidity assay can distinguish whether primary infection has occurred and the chance of a debilitating CMV infection. IgG can be detected using an ELISA test.

Timing of treatment

In the HSCT setting, there are three paradigms for addressing viral infections: prevention, preemptive therapy, and treatment of the disease.

- **Prophylaxis:** Prophylactic prevention is the administration of an antiviral to at-risk patients to avoid reactivation of a latent virus. Preventative therapy is usually avoided because of the toxicity of currently available drugs, even though it is generally considered the ideal CMV prevention paradigm. Many studies suggest allowing viral replication and viremia even without disease can place the bone marrow graft at risk or increase the risk of graft-versus-host disease. However, prophylaxis, at least in the solid organ setting, can result in late onset CMV (which occurs after the completion of the prophylactic course of disease).
- **Preemptive therapy:** Preemptive therapy is the initiation of antivirals only after detection of a specific virus in the blood in an asymptomatic patient. Preemptive therapy usually lasts for 3-6 months, which is the period during which the CMV infection has been historically likely to occur. The prognosis of patients who begin treatment for CMV is significantly better if treated within 100 days of infection. Infection can only be detected at least 35 days after exposure to CMV, leaving a smaller window of time to effectively treat CMV. Primary CMV prophylaxis reduces the incidence of CMV disease by 58-80% and CMV infection by 39% and reduces the incidence of acute rejection by 25%.
- **Treatment of active disease:** Treatment involves the initiation of antiviral therapy only after the virus has been detected in an organ system where clinical signs or symptoms are already present. This is the least ideal treatment paradigm as the patient is already experiencing significant morbidity before treatment is begun. Further, this treatment paradigm results in the highest patient mortality and graft rejection.

Prophylaxis is generally regarded as the optimal treatment strategy for CMV disease prevention. Indeed it is the treatment paradigm used most often in solid organ transplants, but cannot be used in bone marrow transplant because of the toxicity associated with current drugs used to treat CMV. The most common drugs cause bone marrow suppression, thereby interfering with graft function. Second line drugs (like cidofovir) are relegated to that status because of potent kidney toxicity. Prophylaxis is generally regarded to be more effective in preventing CMV disease than preemptive therapy

Preemptive therapy has some advantages that include more selective drug targeting, decreased drug cost, and decreased associated toxicities. It may also promote the development and maintenance of CMV-specific cell-mediated immunity. By lowering the viral replication, late-onset CMV that occurs after the cessation of prophylaxis can be prevented. The preemptive approach, however, should be taken with caution. In D+/R- patients, replication kinetics of CMV in already immunocompromised individuals can be very rapid, and viral screening must occur frequently to monitor levels of CMV.

To date, a consensus has not been established for preventative versus preemptive treatment superiority. Preemptive treatment is easier to implement because it does not require frequent blood testing and follow-up results. It has also been shown to be associated with the reduction in indirect effects of CMV, such as acute rejection and risk of other infections. The use of preemptive therapy however exposes all SOT/HSCT transplant recipients to a prolonged course of antiviral therapy. Normally this would be a problem

because of side effects or resistance, but these aren't concerns for CMX001. Although prophylactive therapy reduces the risk of CMV, it does not prevent late onset CMV in some patients. One possible explanation for late-onset CMV is that after receiving CMV prophylaxis immediately after SOT results in patients failing to develop sufficient CMV-specific immunity to allow efficient control of viral replication upon the completion of prophylaxis.

No drugs have yet been approved for the prevention of CMV in HSCT recipients. A safe and well-tolerated antiviral with demonstrated efficacy in prevention settings could provide a new standard of care for immunocompromised patients. This would potentially replace the current practice of frequent monitoring for CMV viremia and the initiation of anti-CMV preemptive therapy after detection.

Current treatment options:

Ganciclovir (GCV)

Ganciclovir (GCV) is similar to CDV in mechanism of action, but CDV does not require viral enzymes for activation (by phosphorylation). GCV is nucleoside analogue of guanosine and a homologue of acyclovir. It inhibits all the herpes viruses and the transformation of normal cord-blood lymphocytes by the Epstein Barr virus. In vivo, GCV is converted to GCV triphosphate, which inhibits DNA polymerases including those of HSV and CMV by competitively inhibiting the incorporation of deoxyguanosine triphosphate into an elongating viral DNA. After the release of pyrophosphate, GCV monophosphate is incorporated into the end of a growing chain of viral DNA, thereby slowing replication. Unlike ACV, it isn't an absolute chain terminator and short subgenomic fragments of CMV DNA continue to be synthesized. All the drug's antiviral effects are due to its ability to inhibit the synthesis of CMV DNA and therefore its replication by slowing the elongation of viral DNA.

Oral bioavailability of GCV is low (5% in fasting conditions, 6-9% after food). GCV is minimally bound to plasma proteins and concentrates in the kidneys. It is eliminated primarily by the kidneys and undergoes glomerular filtration and active tubular secretion. Careful dosage adjustment is required for patients with renal impairment. 1 gram tid is necessary for patients with normal renal function to achieve plasma concentrations sufficiently high with respect to the concentration at which CMV cell growth is restricted.

Valganciclovir

The shortcomings of GCV led to the development of valganciclovir. It has a higher oral bioavailability compared with GCV, which may translate into a lower risk of emergence of antiviral drug resistance if sufficiently high plasma drug concentrations are maintained.

Foscarnet

Foscarnet is a pyrophosphate analog and is a reversible inhibitor of the viral DNA polymerases and HIV reverse transcriptase. The extent of inhibition of these viral enzymes fluctuates with the rises and falls of drug concentrations at the intracellular locations of the enzymes. The reversible inhibition of the target viral polymerases has been shown not to be competitive with the enzyme substrates or with templates. The degree of inhibition of the viral enzymes is not dependent on either intracellular deoxynucleoside triphosphate levels or intracellular template levels. This is in contrast with nucleoside analogues such as acyclovir, GCV, and zidovudine, of which the activity is influenced by the intracellular

levels of endogenous nucleoside triphosphate. Foscarnet can cause significant renal toxicity and electrolyte imbalances.

Acyclovir

Acyclovir is an analogue of 2'-deoxyguanosine. Like GCV, it must be phosphorylated in the host cell to activate the triphosphate form. ACV is a less efficient substrate than GCV, thereby explaining the lower in vitro potency of ACV versus GCV in CMV-infected cells. Oral acyclovir has a bioavailability of 6-10%, which increases to about 55% with the administration of the L-valyl ester of acyclovir. It has a shorter half-life in infected cells, resulting in lower intracellular levels of active ACV. Patients taking ACV are likely to develop resistance to the drug based on mutations in the viral DNA polymerase or UL97 genes. Even though ACV is not potent enough for the treatment of established CMV disease, the ester has been approved in several countries for prophylaxis of CMV infection and CMV disease in renal or heart transplant recipients or in SOT recipients.

Figure 12: CMX001 vs. currently available treatments

	CMX001	Cidofovir (CDV)	Ganciclovir (GCV)	Valganciclovir (vGCV)	Foscarnet (FOS)	Acyclovir (ACV)
Safety and Tolerability	Dirahhea; managed through dose initerruption	Nephrotoxicity, myelotoxicity	Myelotoxicity	Myelotoxicity	Nephrotoxicity	
Route of Administration	Oral	IV, hydration, probenacid	IV	Oral	IV, hydration	Oral, IV
Dosing Schedule and Duration	2x weekly	Weekly	2x weekly	Daily	2x daily	2x daily
Potency (against CMV)	0.001	0.4	3.8	3.8	50-800	>200
Resistance in CMV	None in phase 2 study, rare in vitro	Rare	Up to 10%	Up to 10%	Rare	OCV cross resistance
Spectrum of Coverage for dsDNA Viruses	All 5 families	All 5 families	CMV, HSV, VZV, HHV-6	CMV, HSV, VZV, HHV-6	CMV, HSV	CMV, HSV, VZV, EBV
Regulatory Status	In development	Approved for human use	Approved for human use	Approved for human use	Approved for human use	Approved for human use

Source: Company website
Potency: concentrations of each antiviral required to reduce viral replication by 50% in vitro (effective concentration)
Resistance: emergence of specific mutations in the virus which decrease the antiviral activity of the drug.

Drugs currently in development to treat CMV

Transvax

Transvax is an investigational DNA vaccine designed to prevent the reactivation of latent CMV or introduction of the virus through donor cells or tissues in transplant patients. In June 2013, Vical and partner Astellas initiated a multinational Phase 3 trial of SP0113 in approximately 500 HSCT patients. Plasmid DNA vaccine induces both T-cell and antibody responses by expressing the two antigens pp65 and gB. Pp65 is a major antigen recognized by T cells in CMV-infected individuals. gB protein is a major surface antigen of CMV and a primary target of neutralizing bodies. The gB protein is a major CMV antigen recognized by both the CD4+ and CD8+ T cells in CMV-seropositve patients.

Vical's recent release regarding unsuccessful Phase 3 data for its Allovectin product may cause the consumer market to lose faith in the Vical technology. This could open a new window of opportunity for CMX001.

Letermovir

Letermovir (AIC264) is a viral terminase inhibitor with specific activity for CMV. It is being developed as an oral antiviral for the prevention and treatment of CMV. It was licensed to Merck in 2012, and a Phase 2 study has been completed. Phase 2 showed benefit versus placebo in preventing CMV reactivation during therapy. Resistance was generated in vitro after a single passage. Data does not address post therapy follow-up period. The drug acts late in the HCMV replication cycle by blocking viral replication without inhibiting the synthesis of progeny HCMV DNA or viral proteins. ALC246 interferes with HCMV DNA cleavage and packaging via a molecular mechanism that is distinct from that of other compound classes that target the viral terminase.

Maribavir

Maribavir is an oral antiviral that inhibits CMV protein kinase UL97, thereby preventing viral encapsulation for CMV specifically. The product was discontinued after Phase 3 studies showed no benefit in HSCT and liver transplant patients for the prevention of CMV infection. ViroPharma is now evaluating maribavir in Phase 2 studies for the treatment of refractory CMV infection using three doses, twice daily. These doses are significantly higher than those used in their failed Phase 3 studies, so they may have a more significant effect on CMV. One concern with maribavir is the data on *in vitro* CMV resistance to the drug.

gB/MF59

gB/MF59 is currently in a Phase 2 clinical trial to evaluate its ability to prevent primary infection in adolescent females. This trial is conducted by the National Institute for Allergy and Infectious Diseases, and Sanofi Aventis has rights to the vaccine. It contains recombinant glycoprotein B.

CMX001

Phase 2 data in CMV: Study 201 showed that CMX001 100 mg given twice a week and CMX001 200 mg once weekly were very effective in CMV prevention and also well-tolerated. The twice weekly group showed a ~75% reduction in the amount of CMV disease versus placebo, which was statistically significant. Similar frequency and severity of severe adverse events were seen in the two dosing groups versus placebo group. Very importantly, there was no indication of myelotoxicity or nephrotoxicity associated with CMX001 or reported discontinuations from the study due to these events.

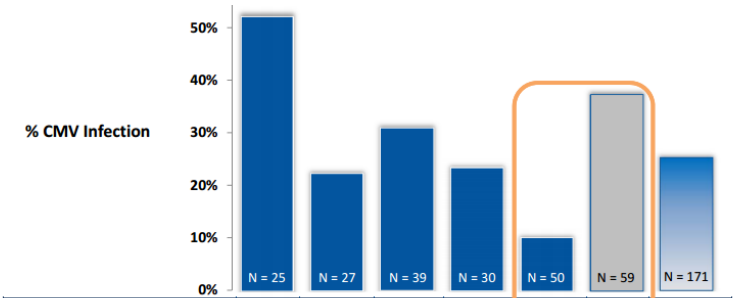
10% of subjects in the CMX001 100 mg biweekly cohort met the primary endpoint of no CMV disease emergence or progression at the end of the dosing period versus 37% in the placebo cohort.

We note that there was unusually high background level of AEs in the patient population that we think is a function of :

1. the severity of the underlying illness and
2. multiple drugs that are administered to HSCT patients both pre- and post-transplant.

GI side effect. The most notable of CMX001's side effects were GI in nature, most commonly diarrhea. 20% of all subjects reported GI-associated events and elevated ALT levels, and the incidence of these reports are generally higher in frequency with increasing doses of CMX001. As such, the FDA limited CMX001 dosing to a maximum of 200 mg or less per week. At 100 mg biweekly, 10% of the subjects discontinued treatment due to GI AEs, compared to 3% in the placebo group. There were cases of transient, dose-dependent increases in ALT and approximately 30% of all subjects experienced ALT increases greater than three times the upper limit of normal(>3x ULT), compared to 16% in the placebo group. However, the ALT increase was not linked to increases in bilirubin or aspartate aminotransferase.

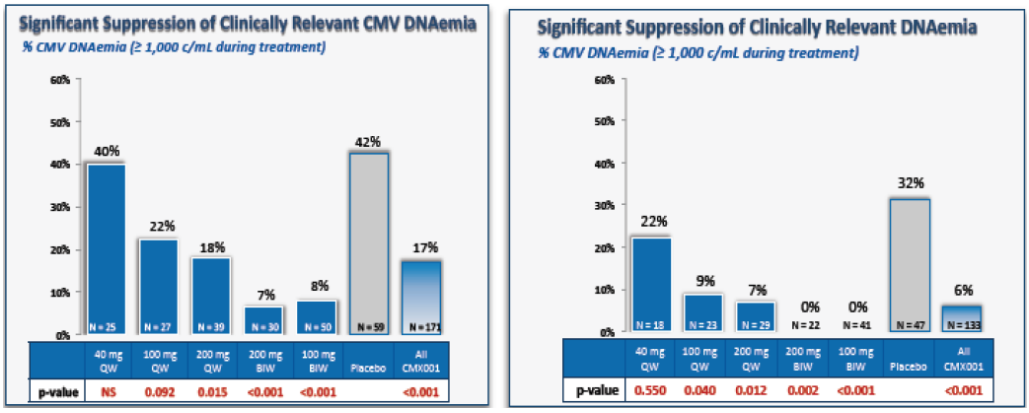
Figure 13: Study 201: >50% decrease in risk of CMV events.
Primary endpoint = CMV disease or CMV PCR>200 copies/mL at end of treatment



	40 mg QW	100 mg QW	200 mg QW	200 mg BIW	100 mg BIW	Placebo	All CMX001
CMV Infection	13 (52%)	6 (22%)	12 (31%)	7 (23%)	5 (10%)	22 (37%)	43 (25%)
p-value	0.234	0.218	0.525	0.235	0.002		0.093

Source: Data from study 201 presented at BMT Tandem, February 2012
Note: QW=dose given once weekly. BIW=dose given biweekly.

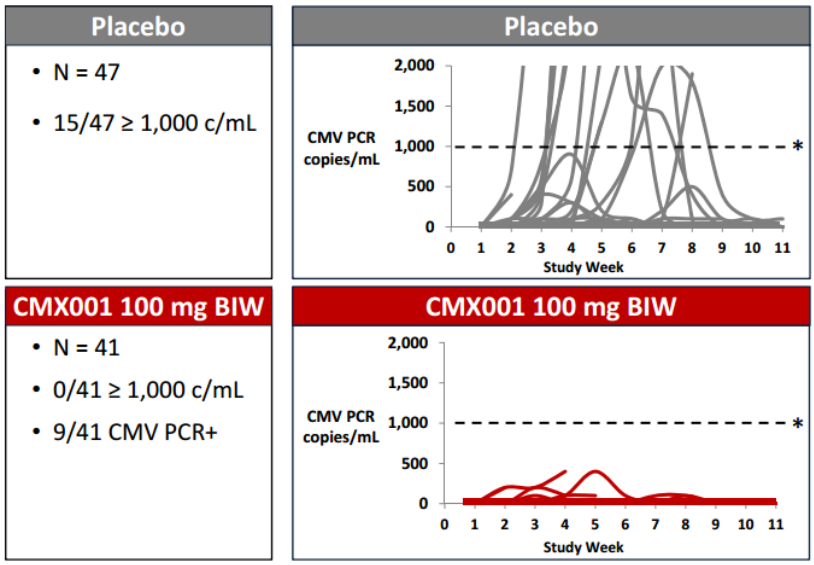
Figure 14: CMX001 prevents or suppresses CMV viremia



Source: Company filing

CMX001 seems to achieve best results in patients without detectible CMV at baseline, and we like that CMRX is taking advantage of this observation in its ongoing SUPPRESS trial by starting therapy sooner, before CMV has a chance to reactivate in the blood.

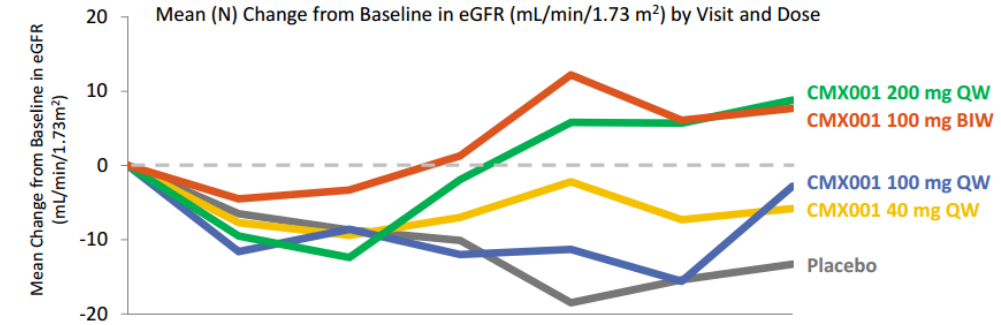
Figure 15: CMX001 suppressed CMV reactivation



Source: Data from study 201 presented at BMT Tandem, February 2012.
Note: * Represents clinically relevant threshold. Subjects CMV negative at baseline.

Figure 15 shows the results from patients receiving 100mg BIW. We think this dosing regimen, which is being advanced in Phase 3, is the one with the most promise as it best balances anti-CMV efficacy with GI side effects. We also note that CMRX has implemented protocol changes and new formulation to improve GI tolerability and these modifications may drive further differentiation versus placebo.

Figure 16: Improvement in renal function with CMX001



Baseline GFR	Week 2	Week 4	Week 6	Week 8	Week 10	Post-Week 1
Placebo	-7 (56)	-9 (46)	-10 (35)	-19 (36)	-15 (21)	-13 (57)
CMX001 40 mg QW	-8 (23)	-9 (19)	-7 (13)	-2 (12)	-7 (5)	-6 (19)
CMX001 100 mg QW	-12 (26)	-9 (25)	-12 (22)	-11 (19)	-16 (13)	-3 (25)
CMX001 200 mg QW	-10 (37)	-12 (31)	-2 (24)	6 (18)	6 (14)	9 (35)
CMX001 100 mg BIW	-5 (49)	-3 (44)	1 (33)	12 (31)	6 (21)	8 (49)
				p=0.0013	p=0.0103	p=0.0025

Source: Data from Study 201 presented at BMT Tandem, February 2013
eGFR: estimated glomerular filtration rate

Mechanism behind lack of kidney toxicity. Cidofovir is transported to kidney cells by uptakes through the HOAT-1 transporter where it accumulates and causes toxicity in the proximal tubule. CMX001, the lipid conjugate of CDF, however, does not enter the kidney cells because it cannot use HOAT-1. Consequently, it does not accumulate and is not nephrotoxic. Study 201 showed no evidence of nephrotoxicity. In fact, CMX001 patients demonstrated a significant dose-related improvement in renal function, which may be related to the drug's activity against a related dsDNA virus, the BK virus, discussed in more detail in a later section.

Figure 17: Overview of Ph2 trial design (Study 201)

Trial	Dose-escalation study of the safety, tolerability and ability of CMX001 to prevent or control cytomegalovirus (CMV) in R+ hematopoietic stem cell transplant recipients
NTC ID	NTC00942305
Condition	CMV infection
Design	Randomized, Safety/efficacy study, Double blind (subject, investigator), Prevention
Treatment Arms	CMX001 (200 mg twice weekly for a total of up to 18 doses), placebo tablets once weekly for a total of up to 11 doses.
Treatment Duration	Up to 9 weeks (CMX001) Up to 11 weeks
Enrollment	150
Key Entry Data	Age ≥ 18 years. Males must be able and willing to use adequate contraceptive methods throughout the treatment and follow-up phases of the study. Females must be postmenopausal, surgically sterile or, for those female subjects of reproductive potential, willing to agree to use two acceptable methods of birth control throughout the treatment phase of the study, with at least one being a barrier method. Allogeneic HSCT recipients who were CMV seropositive before transplantation (i.e., R+ patients). Recipients who are less than 30 days post qualifying transplant. [Note: Under extreme circumstances due to timing issues associated with logistics, patients may be enrolled, i.e. receive first dose of study drug, up to Day 32 post-transplant. Sites must first contact the Chimerix Medical Monitor to receive permission for FDD to be Days 31 or 32 post-transplant.] Recipients must have evidence of engraftment before randomization and receiving their first dose of study drug. Evidence of engraftment will be defined as one of the following: Absolute neutrophil count (ANC) increasing for 3 consecutive days with a count ≥ 500 cells/mm3 by the third day OR Three (3) consecutive days with an ANC ≥ 500 cells/mm3. [Notes: For sites where standard site practice is to monitor white blood count (WBC) early after transplant as opposed to ANC, then engraftment will be defined as WBC increasing for 3 consecutive days with an ANC ≥ 500 cell/mm3 on the third day. For non-myeloablative or reduced-intensity transplants (i.e., mini-transplants) where ANC does not fall below 500 cells/mm3, the site definition of engraftment should be used.] Able to ingest and absorb oral medication (in the judgment of the investigator and based on lack of significant GI events). [Note: Use of TPN (total parenteral nutrition) is not in and of itself exclusionary as long as the reason for use would not disqualify the patient based on this criterion.]
Primary Endpoint	Safety endpoints include clinical assessment and laboratory values, incidence and severity of GvHD, AEs (and SAEs). Efficacy endpoint includes lack of emergence or progression of CMV infection.
Secondary Endpoints	Emergence or increase in CMV DNA. Occurrence of CMV disease. Patient drop-out and/or discontinuation rate. Trough levels of CMX001, CDV, and other metabolites, urine, and/or plasma levels of AdV, BkV, or EBV DNA.

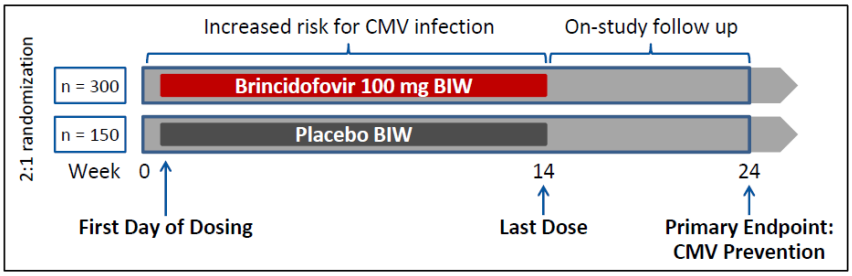
Source: clinicaltrials.gov

Phase 3 SUPPRESS trial

Phase 2 data together with safety experience from expanded access program and emergency INDs strongly support the progression of CMX001 into Phase 3 study for CMX001 in the prevention of CMV in HSCT recipients. Chimerix has recently initiated a pivotal Phase 3 trial (SUPPRESS) that it believes will support conditional Subpart H accelerated approval. SUPPRESS will enroll ~450 patients and randomized to receive weekly doses of CMX001 or placebo. The primary endpoint is CMV prevention through week 24 even though treatment duration is only 14 weeks. The trial design baked in the assumption that 30% of placebo patients and 15% of brin patients will require CMV suppression therapy. We think key secondary endpoints to watch include the evaluation of other dsDNA virus complications, CMV-related opportunistic infections and neutropenia from gancyclovir that will help CMX001 establish a more differentiated profile. Secondary endpoints include pharmacoeconomic data and the incidence of disease and reactivation of other herpesviruses, AdV, and BKV.

Based on our conversations with the company, we think enrollment of the planned 450 subjects is on-track to deliver pivotal data in mid-2015. Positive results from SUPPRESS would be supportive of Subpart H Accelerated Approval of brincidofovir for the prevention of CMV, the first approval of an antiviral for the prevention of CMV in HCT recipients. Likely due to good safety, Chimerix expects the pediatric indication for CMV prevention in US may not require another controlled study. Rather, we think it could be achieved through the submission of safety and PK results generated with commercial formulation.

Figure 18: SUPPRESS: final study design



Trial	A Study of the Safety and Efficacy of CMX001 for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R+) Hematopoietic Stem Cell Transplant Recipients
NTC ID	NCT01769170
Condition	CMV, Adenoviruses (AdV), Epstein-Barr (EBV), Human Herpes Virus Type 6 (HHV6), BK Virus (BKV)
Design	Randomized, Safety/efficacy study, Double blind (subject, investigator), Prevention
Treatment Arms	CMX001 (100 mg twice weekly) or placebo (BIW)
Treatment Duration	As soon as patient can take oral therapy; dosing through Week 14
Enrollment	450
Key inclusion criteria	Subjects will be adult allogeneic HSCT recipients aged ≥ 18 years-old (or as applicable, per local law) who were CMV seropositive before transplantation and are CMV viremia negative posttransplant.
Key exclusion criteria	• Subjects who have a positive CMV viremia test at any time between transplant and the First Dose Day (FDD). • Subjects with hypersensitivity (not renal dysfunction or eye disorder) to CDV or to CMX001 or its excipients. • Subjects who have received any anti-CMV therapy and investigational anti-CMV drugs at any time post-transplant. • Subjects who have had any anti-CMV vaccine at any time.
Primary Endpoint	CMV prevention through Week 24 post-transplant
Secondary Endpoints	Prevention of other dsDNA virus diseases (AdV, BKV, EBV, HHV-6, HSV, VZV); kidney function; CMV-related infections; ganciclovir-related neutropenia; healthcare utilization
Powering	>87% to detect relative 50% reduction in CMV events versus placebo (estimated at 30%)

Source: Company website

We think SUPPRESS is well-designed and the allowed pre-engraftment dosing (enabled by lack of bone marrow tox signal in the Phase 2) will achieve a concentration early post-transplant, which allows capture of early CMV events for placebo patients. This should allow SUPPRESS to show an increasing difference in event rate for brincidofovir cohort versus placebo over 14 weeks.

Managing GI side effects: CMRX's implementation of a safety monitoring and management plan (SMMP) may also help manage GI symptoms or ALT elevations in patients receiving brincidofovir. We note the SMMP used in CMX001-201 has been revised to recommend interruption of study drug upon occurrence of Grade 2 diarrhea that persists for more than three days, if the diarrhea is associated with decreases in serum albumin. The decrease in albumin is thought to be related to the diarrhea. Based on previous clinical experience, if the diarrhea persists for 72 hours after dose interruption, the cause is likely graft-versus-host disease. In such a case, the physician is allowed to put the patient back on brincidofovir treatment. If the diarrhea resolves, patients are allowed to restart

brincidofovir under a titration regiment. Persistent Grade 3 diarrhea calls for mandatory dose interruption regardless of albumin. We note that 23% of patients in Study 201 required hospitalization for SAEs and 14% switched to second-line therapy due to toxicity.

We think SUPPRESS could highlight CMX001's broad spectrum activity and other benefits such as its lack of toxicity on bone marrow and kidney versus other CMV therapy. If brincidofovir shows reduced need for preemptive therapy and as a result demonstrates a benefit on some of the secondary endpoints, the label of brincidofovir could be vastly improved. We think this would have a significant impact on price point and market penetration in HSCT; prospects for expansion into other settings such as solid organ transplant may also be more favorable.

Data from Phase 2 trials and the expanded access program showed dose-related improvement in renal function and evidence of clinical benefit against BKV. We note patients who harbor BKV at baseline showed a more significant benefit. We think CMX001 may also decrease non-relapse mortality to less than 20% through prevention of composite clinical events due to other dsDNA viruses. We think CMX001 could also show a decrease in need for preemptive therapy and thereby decrease rehospitalization rates and the known toxicities associated with ganciclovir and foscarnet.

Figure 19: CMX001 toxicities in patients receiving preemptive Tx with ganciclovir or foscarnet

Bone marrow toxicity	– 70% had moderate-to-severe decreases of white blood cells – 41% experienced low ANC with risk of fungal and bacterial infections – 15% required G-CSF; 7% RBC transfusions; 3% platelet transfusion
Kidney toxicity	– 25% experienced decrease in kidney function
Severe Adverse Events (SAEs)	– 23% required hospitalization for SAEs – 14% switch to second line therapy due to toxicity

Source: ICAAC, September 2012

We think SUPPRESS will read out in mid-2015 and we expect news flow this year to focus primarily on enrollment updates. With that said, we are not discounting the possibility of a surprise in timeline given strong enthusiasm we have seen from our conversations with KOLs. We note that brincidofovir has been used in more than 200 patients under an Emergency IND and an expanded access program in another 200 patients encompassing a range of dsDNA virus indications. We look forward to seeing the data CMRX has on hand for brin in other viral settings such as active CMV disease, PML, neonatal herpes encephalitis, and refractory warts. We expect CMRX to publish some of these datasets in 2014, which would help us identify other markets for CMX001, and we expect these publications to help CMRX secure a broader label for brincidofovir beyond the stem cell transplant setting.

CMX001 in solid organ transplant

Just like in patients undergoing bone marrow transplant, CMV also has a deleterious impact on patients undergoing solid organ transplantation (SOT). CMV adversely affects both graft organ functions and increases morbidity and mortality. Patients with CMV may develop asymptomatic viremia (detectable levels of virus in the blood), CMV syndrome (flu-like symptoms caused by CMV infection) or tissue-invasive disease. High-risk patients who receive prophylaxis often develop late-onset CMV disease after the cessation of prophylaxis.

The CMV risk of a solid organ transplant patient is determined by a number of factors including:

- The CMV serostatus of the donor-recipient pair
- the types of organ or organs transplanted
- the type and/or state of immunosuppression of the transplate patient

Serostatus: CMV seronegative patients (R-) who receive an organ transplant from CMV seropositive donor (D+) have the highest risk of primary CMV disease as latent virus in the graft tissue is highly likely to be reactivated in the recipient because the recipient's immune system has no inherent immunity against CMV. This may trigger a primary infection of the recipient as well as potential reactivation and disease in the graft organ. Further, standard post-SOT immune suppression to inhibit graft rejection also hinders the recipient from mounting an effective immune response against the CMV. This is also the reason that CMV+ recipients (either R+/D+ or R+/D-), who should have CMV immune memory, are also at risk for CMV disease, regardless of graft serostatus. R-/D- have the lowest risk.

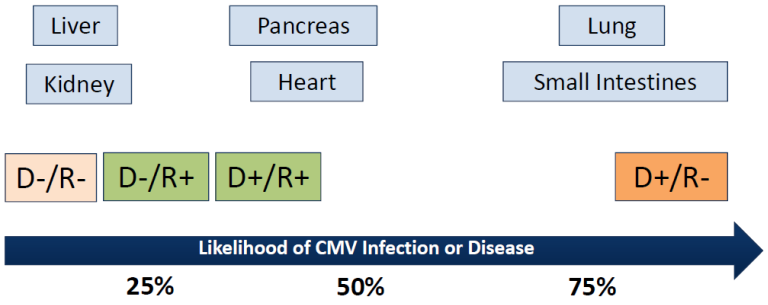
Transplant type: Lung and intestine transplant recipients are at a higher risk than kidney and liver transplant recipients of acquiring CMV disease. This is hypothesized to be related to overall amount of tissue and specifically the amount of lymphoid tissue (where latent CMV resides) that was transplanted. This sheer volume of infected tissue has an impact on CMV risk. Further, these recipients also generally receive stronger immunosuppression.

Immunosuppression of recipient. Severely immunocompromised transplant patients are also at elevated risk of CMV disease. Patients' degree of immunosuppression is dependent on a number of factors including the dose, duration and type of immunosuppressive agents. Studies have also shown host immune defects, whether innate or adaptive, age-related, as well as underlying comorbidities, may also play a significant role. T-lymphocyte depleting immunosuppressive agents – e.g., anti-lymphocyte globulin (ALG), anti-thymocyte globulin (ATG), OKT3 (anti CD3 antibody) and alemtuzumab (anti-CD52 antibody) – are associate with delayed immune reconstitution and CMV immune response. These drugs have also been associated with elevated risk of CMV disease when used for acute allograft rejection.

Recent studies have identified close cause-and-effect relationship between CMV and allograft rejection that can go both ways. Organ rejections can create a hyper-inflammatory environment that can lead to CMV reactivation. Treating rejection hinders the recipient's immune response to inhibit viral replication. As a result, rejection is often seen in late-onset CMV disease in D+/R- liver and kidney transplants. Even worse, CMV proactively upregulates antigens on the graft, which can cause alloreactivity, leading to rejection of the allograft.

D-/R- patients, meanwhile, carry the lowest risk of CMV disease. DeFilippis et al found the incidence of CMV disease in this population is close to 1-2% at 12 months after transplantation, largely the result of primary infection.

Figure 20: Risk of CMV infection following solid organ transplant



Source: Razonable, 2013

Newer generation immunosuppressants may have reduced risk of CMV infection. Poglitsch et al suggest mTOR inhibitors such as everolimus are associated with a lower risk of CMV infection and disease. The study also found herpes virus co-infection, especially HHV-6 and HHV-7, may predispose patients to CMV.

Prevention of CMV diseases in solid organ transplant (SOT)

The two major strategies used to prevent CMV disease in SOT are antiviral prophylaxis and preemptive therapy (Figure 21). Clinicians sometime use a hybrid approach: administering prophylaxis during the initial high-risk post-transplant period, and afterward, during the modest-risk period, monitoring for viremia and using preemptive therapy when needed.

Figure 21: Strategies for CMV disease in SOT

Parameters	Pre-emptive therapy	Antiviral prophylaxis
Cost	Increased laboratory cost	Increased drug related cost
Ease of coordination	Difficult to coordinate lab draw, follow up of results and time-appropriate action	Easier to coordinate, however drug toxicity needs to be monitored
Drug toxicities	Lower	Higher
Protection against other Herpes viruses	None	Yes
Protection against "Indirect" effects	Less	Yes
Development of CMV specific immunity	+	–
Incidence of late onset CMV	Low	High in D^+/R^-
Antiviral resistance	+	+
"Escape" infections	Can occur due to rapidly replicating virus	No (breakthrough infections may occur in patients receiving suboptimal dosing)

Source: Razonable, 2013

Antiviral prophylaxis: Prophylaxis involves dosing all at-risk patients with antivirals starting sometime during the first 10 days post-transplant and for a duration of three to six months. Prophylaxis can also protect patients from other herpes virus infections. It has also been associated with lower rates of indirect CMV effects such like graft rejection, opportunistic infections and mortality.

However, current antivirals such as ganciclovir or valganciclovir have serious toxicities like leukopenia and neutropenia. Further, late-onset CMV disease often emerges after the prophylaxis regimen is stopped.

Valganciclovir is the most commonly used antiviral despite its kidney (and possible liver) toxicity. Oral ganciclovir and IV ganciclovir are sometime used as well. Valacyclovir is used primarily in kidney transplants: it is has higher oral bioavailability and lower pill burden than oral ganciclovir, but it does not have as broad anti-double stranded DNA virus activity. Liver transplant patients on valganciclovir tend to have more tissue invasive disease versus those on oral ganciclovir. This is why valganciclovir was never approved for CMV prophylaxis in liver transplant patients. And yet, valganciclovir is still the preferred prophylactic drug in liver transplants.

Duration of prophylaxis treatment is dependent on the type of organ transplant and donor/recipient serostatus. The IMPACT trial compared the efficacy of 200 days of valganciclovir prophylaxis versus 100 days in D+/ R- kidney transplant recipients. Trial data showed the 200 days' treatment group had significantly lower rates of late-onset CMV disease. Standard valganciclovir prophylaxis is now used for 200 days in D+/R- kidney recipients with high CMV risk. Longer durations of valganciclovir prophylaxis are also now widely used by the liver, heart, pancreas transplant programs across the country.

In a separate study of the incidence of lung transplant-related late-onset CMV, patients on 52 weeks of prophylaxis had significantly lower rates of CMV disease and appeared to have a durable CMV protective benefit. As a result, clinicians now give D+ lung transplant patients prophylaxis for 52 weeks. Some centers even give adjunctive CMV-specific IV immunoglobulin layered onto prophylaxis to lung and heart transplant recipients.

One of the main drawbacks of preemptive therapy for CMV is the close monitoring required of patients by either pp65 antigenemia assay or Quantitative Nucleic Acid Test (QNAT) once a week for three months post-transplant.

Preemptive therapy is, however, associated with decreased drug-related toxicities as well as drug costs. Further, and of high importance, is the fact that many KOLS believe patients develop CMV-specific immunity during exposure to low-level CMV viremia, which leads to lower rates of late-onset CMV.

Figure 22: Preferred and alternative drugs active against CMV in SOT

Preferred Drugs	Antiviral prophylaxis	Treatment	Side effects/Remarks
Valganciclovir	900 mg PO once daily	900 mg PO twice daily	Bone marrow suppression - Leucopenia
Ganciclovir IV	5 mg/kg once daily	5 mg/kg twice daily	Bone marrow suppression - Leucopenia
Alternative drugs	**Antiviral prophylaxis**	**Treatment**	**Side effects/Remarks**
Oral ganciclovir	1 g PO thrice daily	Not recommended	Leucopenia, high pill burden Induction of resistance
Valaciclovir	2 g PO four times daily	Not recommended	Only in kidney recipients Second line even in kidney SOT High pill burden
Foscarnet	Not recommended	60 mg/kg IV every 8 h or 90 mg/kg every 12 h	Used in high level UL97 mutant ganciclovir resistance Nephrotoxic
Cidofovir	Not recommended	5 mg/kg once weekly × 2, followed by q 2 weeks thereafter.	Used as alternative drug in UL97 mutant ganciclovir resistance Nephrotoxic

CMV, cytomegalovirus.; PO, per oral; SOT, solid organ transplantation..

Source: Razonable, 2013

On the other hand, the cost for weekly monitoring associated with preemptive therapy is very high. Further, it does not protect against other herpes co- infections. Care burden is also high: preemptive therapy patients have multiple lab, clinic, and follow-up visits.

In addition, CMV infection in high-risk individuals can often progress rapidly, and may not be captured early-on by weekly lab tests. Also, there is no established viral load threshold to guide preemptive therapy. Martín-Gandul et al suggested a viral load of 3,983 IU/mL should be the cut-off for starting preemptive therapy in CMV-seropositive patients.

Preemptive therapy patients are treated with either bid oral valganciclovir 900 mg or bid intravenous ganciclovir at 5 mg/kg. Treatment continues until the viral load drops below a predetermined threshold determined by the clinician or transplant center.

Prevention of late-onset CMV disease

Clinicians see the biggest drawback of prophylaxis as CMV disease that occurs after the complete course of treatment, the "late-onset CMV" mentioned previously. D+/R- SOT recipients are at the highest risk. Various centers have taken steps to reduce this risk by adopting a hybrid approach described previously. However, studies showed 41% of these patients still developed CMV disease.

Treatment of CMV disease

Standard treatment of viremia and disease: The two main treatment options currently used are IV ganciclovir at 5-mg/kg given q12 hours and 900-mg oral valganciclovir BID. Oral valganciclovir is the preferred treatment for mild to moderate CMV. IV ganciclovir is used to treat life-threatening CMV or very high viral load disease. Duration of therapy is individualized and determined by resolution of clinical symptoms and viral load.

Resistance to current antivirals: Ganciclovir-resistant CMV has been increasing although it is still relatively unusual. Patients with ganciclovir-resistant CMV have increased morbidity and mortality. Incidence seems to be highest among lung transplant recipients. Virus with mutation in UL97 phosphotransferase and UL54 DNA polymerase are the two most common variants that induce drug resistance in CMV.

The first phosphorylation/activation step of ganciclover triphosphate is mediated by a viral kinase encoded by UL97; UL97 mutations may lead to ganciclovir resistance. Mutations in UL54 are less common and usually occur after UL97 mutation. Ganciclovir triphosphate prevents viral replication by competitively inhibiting UL54 DNA polymerase gene; therefore, combined UL54-UL97 mutations render high-level resistance to ganciclovir.

Clinicians suspect resistance in patients with rising or breakthrough viral load after three weeks of therapy. In patients with low-level UL97 resistance, the preferred treatment is increased IV ganciclovir dose (10mg/kg bid). In high-level ganciclovir resistance, Foscarnet is the preferred drug. Switching immunosuppressive regimens to certain mTOR-based regimes or reducing overall immune suppression may also help.

Figure 23: Risk factors for development of ganciclovir resistant CMV

D^+/R^- CMV serostatus
Lung transplantation
Increased intensity of immunosuppression
High pre-treatment CMV viral load
Prolonged subclinical viremia
Previous exposure to sub-therapeutic doses of valganciclovir or ganciclovir

Source: Razonable, 2013

Opportunity for CMX001 in solid organ transplant

We think an improved safety and tolerability profile (particularly reduced kidney toxicity) of an antiviral agent could shift usage more toward universal prophylaxis versus monitoring and preemptive therapy, even in moderate risk patients, and particularly in kidney transplants. We expect the broad- spectrum activity of brincidofovir to be supported in future studies and we think these results could drive uptake in SOT, particularly in the renal transplant settings.

ADENOVIRUS IN TRANSPLANT RECIPIENTS

ADENOVIRUS (ADV)

AdV are divided into seven sub-species. A total of 52 subtypes have been identified, of which, 1, 2, 5, 7, and 14 are the most common cause of infection. Adenoviruses are highly resistant to physical and chemical agents. They remain infectious for long periods, conferring high virulence. Nosocomial infections and outbreaks have been reported. Adenovirus becomes latent in lymphocytes after primary infection and reactivation is implicated in most cases of adult disease. As expected, primary infection is more common in children.

Adenoviruses have many mechanisms for evading host immunity. They inhibit interferon function by virally associated RNA and E1A. They inhibit intrinsic cellular apoptosis in infected cells, and also prevent cell surface MHC-I antigen expression. Humoral immunity is also key in controlling AdV infection. Bone marrow transplant patients with adenovirus viremia have increased levels of serotype-specific antibodies after resolution of infection.

AdV can be life-threatening in immunocompromised patients, particularly after bone marrow transplants. Frequent reinfections and viral persistence in children as well as the presence of AdV specific CD4+ T cells in asymptomatic adults suggest adequate cross-reactive immune protection against AdV takes years to develop. Latent virus dwells in lymphoreticular tissue (e.g., macrophages in tonsils, adenoids, and intestines). Viral shedding can last months to years, even in healthy children, making horizontal transmission a serious risk to immunocompromised patients.

Adenovirus disease among immunocompetent patients is rare and self-limited. It typically manifests as mild upper respiratory, gastrointestinal, or conjunctival disease. In

immunocompromised patients, however, it can cause a wide spectrum of disease with more organ involvement, disseminated disease, and higher mortality. In the bone marrow transplant setting, adenovirus disease can manifest as mild to life-threatening upper and/or lower respiratory tract infection (e.g., pneumonia), gastrointestinal disease (hemorrhagic colitis), hepatitis or cystitis.

Adenovirus infection incidence has increased in the past decade due to a number of factors including:

- greater awareness
- aggressiveness of immunosuppressive conditioning regimens
- greater sensitivity of diagnostic methods
- More widespread screening.

AdV disease rates range from 5% to 47% and can depend on a patient's risk profile. This in turn can depend on patient age, conditioning regimen, type of diagnostic method, and clinical sample analyzed.

Risk factors for AdV viremia include:

- Age
- allogeneic transplant
- T-cell depletion conditioning regiments
- unrelated or HLA-mismatched grafts
- total body irradiation
- low T-cell count after transplant

Bone marrow transplant related AdV mortality rates can range from 12% to >60%. Most adult bone marrow patients with a disseminated AdV infection only exhibit transient viremia and only rarely develop AdV disease.

Risk factors for adenovirus disease include:

- the number of sites (or organs) in the body where AdV can be detected
- type of immunosuppressive therapy
- lymphocytopenia
- level of viremia
- Rising viral load in the blood

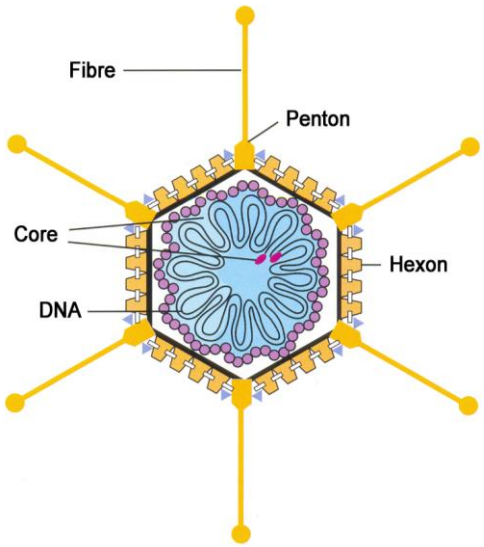
AdV viremia is usually detected within 100 days post-transplant with a mean of 58 days, although this can range from 44 to 333 days.

AdV infections is much more serious in pediatric patients undergoing both bone marrow and solid organ transplant than in adults, largely because of much higher morbidity and mortality. Disseminated (detected in 2+ organs) disease is about 1-7% in these pediatric patients and is associated with a mortality rate of 8-26%. Weekly RT- PCRs are done in

these patients to monitor AdV, SMV, EBV, and HHV-6 DNA load, and rate of immune-reconstitution (CD3 counts) after bone marrow transplant.

Although AdV infection occurs much less frequently than CMV in the transplant setting, it has a higher mortality rate, making it of high concern especially in kids. There are no current approved therapies available for AdV prevention, preemptive therapy or even treatment.

Figure 24: Structure of AdV



Source: http://biomarker.korea.ac.kr/pathogen/pathogen_view_en.jsp?pclass=2&id=15

AdV Infection

Adenovirus particle uptake occurs in two-stages: an initial interaction of fiber protein with cellular receptors (e.g. MHC-I complex, coxsackievirus-adenovirus receptor) and then penton base protein binding to integrin binding. This binding causes internalization via receptor-mediated endocytosis.

Detection and diagnosis

AdV diagnosis can involve virus culture, antigen-based methods (immunofluorescence, enzyme immunoassays, or immunochromatography), or nucleic acid amplification tests (NAATs). PCR, however, is the cheapest, most rapid and accurate and therefore favored method of diagnosis. Real-time PCR can detect AdV in as low as 10 to 10^6 copies of viral DNA in a sample. PCR can be performed in the blood, stool, sputum, and biopsy specimens. Quantitative viral load measures are key to the diagnosis of infection and to determining prognosis. Higher viral loads (>1x10^6 copies/mL) are associated with higher mortality.

The definition of infection is controversial as viremia does not always correlate with clinical symptoms. Adenovirus disease is defined as symptoms/signs suggesting infection with no other attributable cause, together with histological documentation of AdV and/or culture, antigen test, or nucleic acid test from biopsy specimens, broncheoalveolar lavage fluid, or cerebrospinal fluid showing presence of AdV. Disseminated disease is documented

disease in two or more organs. Virologic response is defined as >99% decrease in plasma viral load from baseline or undetectable viral load by the end of treatment or follow up period.

Current lines of treatment: cidofovir and ribavirin

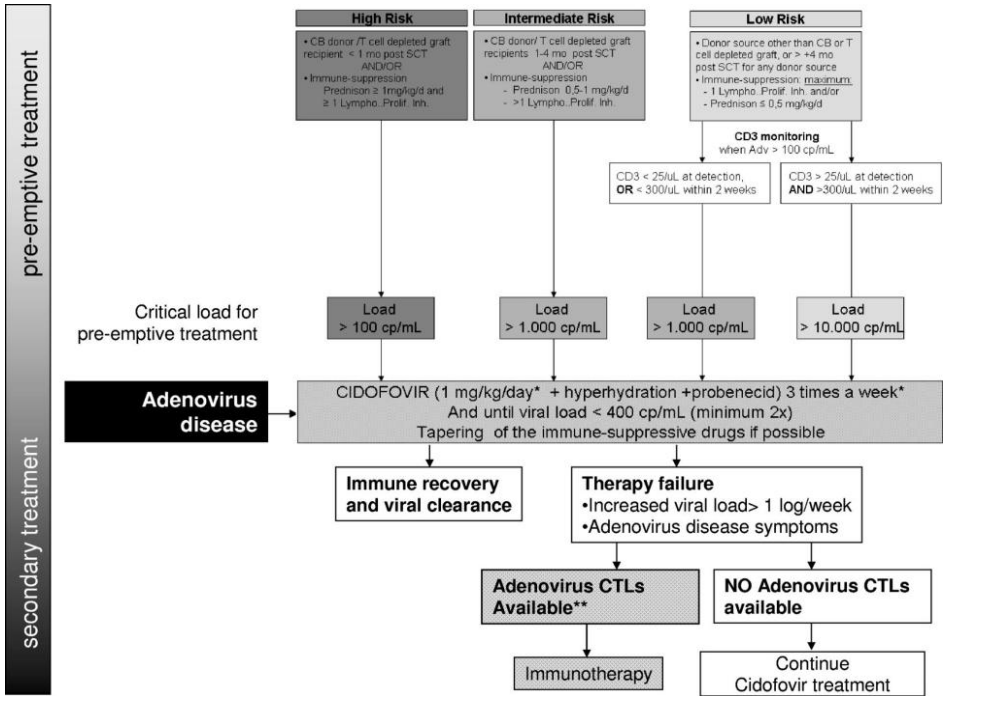
The current gold standard treatment for AdV is cidofovir (CDV) or ribavirin (RBV), with better evidence for use of CDV than RBV. The mechanism for inhibition of viral DNA polymerase and viral replication is similar to CMV. Antiviral selectivity of these drug is driven by their higher affinity for viral DNA polymerase than cellular DNA polymerase. CDV diphosphates compete with nucleotide triphosphates. They are more efficiently incorporated into viral DNA, inhibiting viral replication. CDV has a low bioavailability, which is a problem since antiviral effect depends on active phosphorylated metabolite concentrations in infected cells. >90% of CDV is excreted unchanged in the urine. While CDV is the most effective AdV antiviral agent, it is also the most toxic due to kidney toxicity. Hyperhydration and co-administration of the drug probenecid are almost always used to moderate cidofovir's kidney toxicity. Probenecid is a nephroprotective organic acid that competes for the kidney's organic anion transporter (HOAT-1) and protects tubule cells.

Ribavirin is a purine nucleoside analog with in vitro activity against DNA and RNA viruses. It is phosphorylated intracellularly, and inhibits inosine monophosphate dehydrogenase, causing reductions in intracellular GTP pools, inhibition of initiation and elongation by viral dependent polymerases, and interference with mRNA capping. Treatment success is closely related to early treatment and AdV serotype. The most common AE is reversible mild anemia.

Timing of treatment

Patients who received ribavirin preemptive treatment have lower incidence of AdV infection (29% vs. 66%) and AdV associated mortality (0% vs. 14%). AdVs, unlike herpesviruses (e.g CMV) do not encode a kinase which makes them insensitive to acyclic nucleoside analogues.

Figure 25: Current treatment guidelines for AdV



Source: http://www.ncbi.nlm.nih.gov/pubmed/20837781
Lympho. Proilf. Inh.=lymphocyte proliferation inhibitor (eg cyclosporine A, CsA).
*=alternative cidofovir f mg/kg intravenously weekly.
**=for centers that have AdV CTLs readily available, CTLs are immediately initiated for all high-risk patients for all patients with AdV symptoms before cidofovir effect.

CMX001 in AdV: Phase 2 data from Study 202

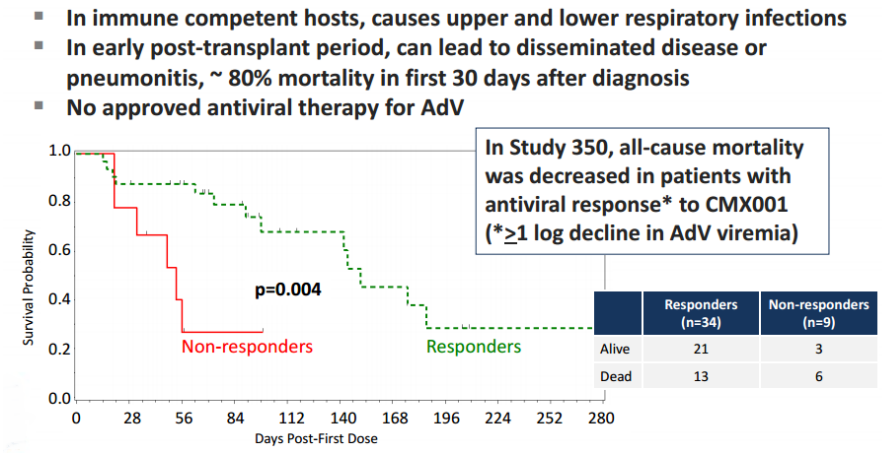
CMRX's Study 202 in AdV was initiated in July 2011. The placebo-controlled, multi-site trial looked at CMX001 as a preemptive therapy for AdV disease in hematopoietic stem cell transplant (HSCT) recipients. Endpoints included safety, tolerability, and efficacy of weekly and biweekly regimens of CMX001 versus placebo (BIW or QW dosing for 6 to 12 weeks).

These were measured in 36 pediatric and 12 adult HSCT transplant recipients with asymptomatic AdV viremia at 29 US transplant centers. Subjects received CMX001 or placebo BIW or QW for 6 to 12 weeks at 100 mg BIW or 200 mg QW for adults (tablet), or at 2 mg/kg BIW or 4 mg/kg QW for children (liquid). Subjects undetectable for AdV viremia for at least six consecutive weeks were considered as having complete response and progression rate from AdV viremia to AdV disease was assumed to be 50% for purposes of powering study.

The primary efficacy endpoint of the study is treatment failure: a composite endpoint consisting of (i) progression to probable or definitive AdV disease, or (ii) increasing AdV viremia during randomized therapy that requires discontinuation from randomized therapy. Secondary endpoints – including incidence and time to mortality, the percentage of subjects on randomized therapy with undetectable plasma AdV PCR measured at various time points, and the percentage of subjects who have emergence or progression of CMV, EBV, or BKV viremia or disease during therapy – were measured.

We have seen in previous studies that failure to achieve a > 1 log(10) decrease in viral load during the first two weeks of therapy is associated with poorer patient outcomes and we saw in Expanded Access Study 350 that all-cause mortality decreased in patients with an antiviral response to CMX001 with a ≥1 log decline in AdV viremia.

Figure 26: CMX001 and adenovirus



Source: Data from study 350 presented at European Group for Blood and Marrow Transplantation (EMBT), April 2013.

Study 202 data showed CMX001 100mg BIW produced a rapid decrease in viremia in AdV patients with high baseline viral load, and a trend toward lower all-cause mortality. These data suggest CMX001 is an effective AdV antiviral. However, the study's primary endpoint, the proportion of patients with treatment failure, did not reach statistical significance (21% for CMX001 BIW vs 33% for placebo, p=0.45), despite strong numerical trends in the data. The definition of treatment failure was either progression to probable or definitive AdV disease, or confirmed increase from baseline in AdV viremia by 1 log(10) during blinded therapy. CMRX thinks the trial may have allowed too liberal a definition of progression, as clinicians knew that treatment failures could roll over onto active treatment. Further, we think statistics were also confounded by the relatively high lower limit of detection in the AdV PCR assay. CMRX expects future trials may test prophylactic rather than preemptive therapy, and will probably examine progression driven by a number of dsDNA viruses.

Figure 27: Study 202 AEs of interest (all grades) in ITT population

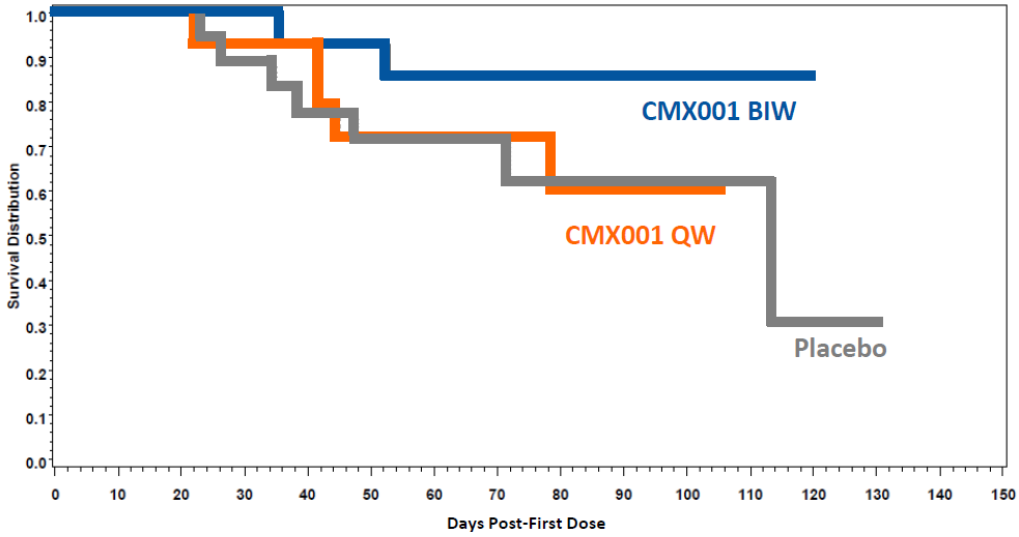
	CMX001 BIW n=14	CMX001 QW n=16	Placebo n=18
Renal			
Renal failure	2 (14%)	1 (6%)	1 (6%)
Hematuria	0	0	2 (11%)
GI			
Diarrhea	8 (57%)	6 (38%)	5 (28%)
Nausea	2 (14%)	2 (13%)	4 (22%)
Vomiting	1 (7%)	4 (25%)	4 (22%)
Abdominal pain	2 (14%)	0	2 (11%)
Hematologic			
Neutropenia	1 (7%)	1 (6%)	2 (11%)
Anemia	1 (7%)	1 (6%)	0
Thrombocytopenia	2 (14%)	0	0

Source: Company reports

Study 202 showed no new safety concerns and had similar rates of discontinuations for AEs across dosing groups. We think the early discontinuation rate was likely influenced by availability of open-label CMX001. There were also no hematology concerns as the one patient with graft failure during trial was on placebo. Successful implementation of the SMMP decreased permanent discontinuations due to diarrhea compared with previous studies, and there was no differences in ALT elevations among the three groups. There were also no differences in renal function over the course of therapy between the three cohorts, although we note that one patient on CMX001 BIW developed renal failure after completion of therapy.

Figure 28: Study 202 primary endpoint and all-cause mortality rate

Primary Endpoint	CMX001 BIW n=14	CMX001 QW n=16	Placebo n=18
Subjects with treatment failure	3 (21%)	6 (38%)	6 (33%)
Increase in viremia only	1	1	1
Evidence of end-organ disease +/- increasing viremia	2	5	5
p-value (versus placebo)[a]	0.450	0.779	N/A



Source: Company reports

We note there was favorable numerical difference between CMX001 BIW and placebo for AdV progression and for all-cause mortality, and that AdV was not reported to be the primary cause of death in any subject (although some patients had AdV or other dsDNA viruses at the time of death). We also note that AdV viremia does not seem to be an appropriate indication of "early" AdV disease or a "trigger" for initiation of preemptive therapy, as low level of AdV viremia is often spontaneously cleared, particularly in lower-risk patients. Besides, emergence of AdV viremia is usually correlated with end organ disease, yet the ability to detect AdV in blood may not precede AdV end organ disease. The trial results give us confidence that even though a singular role of AdV on mortality might be difficult to demonstrate in a patient population at risk of multiple dsDNA viral infections, we have seen anecdotal evidence of broad spectrum activity of CMX001 and it

may translate into positive clinical impact on other causes of non-relapse mortality. We think the data, though not hitting statistical significance, is supportive of continued development of CMX001 for prevention of dsDNA viruses in at-risk transplant recipients.

Figure 29: Overview of Phase 2 trial design (Study 202)

Trial	The AdV HALT trial (Study 202)
NTC ID	NCT01241344
Condition	Adenovirus Disease
Design	Randomized, Safety/efficacy study, Double blind (subject, investigator), single group assignment, treatment
Treatment Arms	Adults: 200 mg CMX001 given as four 50 mg tablets orally either QW or BIW. Pediatric: 4 mg/kg (NTE a total single dose of 200 mg) given using 5 mg/mL liquid formation taken orally either QW or BIW. Placebo: Adults: two matching placebo tablets taken orally QW or BIW. Pediatric: Matching liquid placebo taken orally QW or BIW.
Treatment Duration	One single dose
Enrollment	48
Key Entry Data	• Males or females of non-childbearing potential, 18 to 55 years of age. Males must be able and willing to use adequate contraceptive methods throughout the study.
Primary Endpoints	Evaluate the safety and efficacy of preemptive treatment with CMX001 versus placebo for the prevention of AdV disease in recipients of HSCT with asymptomatic AdV viremia. The outcome measure for the primary endpoint will be treatment failure. Treatment failure is the composite endpoint consisting of: • Progression to probable or definitive AdV disease • OR increasing AdV viremia during randomized therapy (defined as increase from baseline in AdV viremia by ≥ 1 log10, confirmed on a second measurement, at least one week apart) AND requiring discontinuation from randomized therapy
Secondary Endpoints	• To compare the safety and efficacy of two dosing regimens of CMX001 versus each other and versus placebo in this indication. • To compare the incidence of treatment emergent dsDNA viral infections (other than those caused by AdV), in subjects treated with CMX001 QW versus CMX001 BIW versus placebo, initially, for the preemption of adenoviral disease. • To characterize the safety and efficacy of CMX001 open-label therapy in patients who meet the primary endpoint of treatment failure during randomized therapy.

Source:Clinicaltrials.gov

BK VIRUS (BKV)

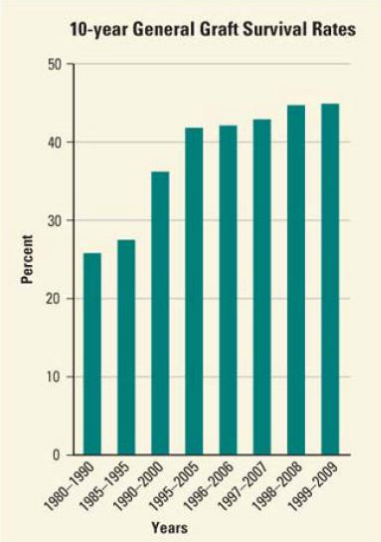
Polyomavirus BK is a nearly ubiquitous dsDNA virus with high prevalence rates (by seropositivity) in the general US population. Following primary infection, BK virus latently resides in the reno-urinary tract (i.e., kidneys and urethra). Reactivation usually occurs in normal subjects with asymptomatic viruria (virus in the urine). However, in select cases, it can also be associated with nephropathy (PVAN, or polyoma virus-associated nephropathy) in kidney transplants. PVAN develops in ~10% of renal transplant patients. Approximately 65% of these patients will lose their transplanted kidney as a result of PVAN.

PVAN is one of the most common viral complications in kidney transplants and a key cause of renal transplant dysfunction and graft loss. Many KOLs believe the increase in prevalence is linked to new, strongly immunosuppressive drugs.

PVAN is usually diagnosed in the first year post-transplant, although approximately 25% of the cases emerge later. Clinical presentation may be subtle. Varying degrees of kidney dysfunction may be seen, but in early stages there may be normal serum creatinine levels.

PVAN often lead to interstitial nephritis, ureteric stenosis with ureteric obstruction, hydronephrosis, and periodic urinary tract infections. Progressive renal failure is reported in approximately 45% of the cases. Most PVAN cases are preceded by an asymptomatic phase of persistent and significant viruria. Sustained BK viruria is usually followed by viremia within a few weeks. A significant and sustained viremia, clinically identified as >5000 copies/mL plasma for three consecutive weeks, identifies patients with uncontrollable viral replication that may lead to parenchymal injury.

Figure 30: BKV continues to impact renal transplant survival



- **Although graft survival has improved, 10-year graft survival is still <50%**
- **~20% of renal transplant recipients have BK viremia in the first year post-transplant**
- **BKV-associated disease results in graft loss in 65% of affected patients**

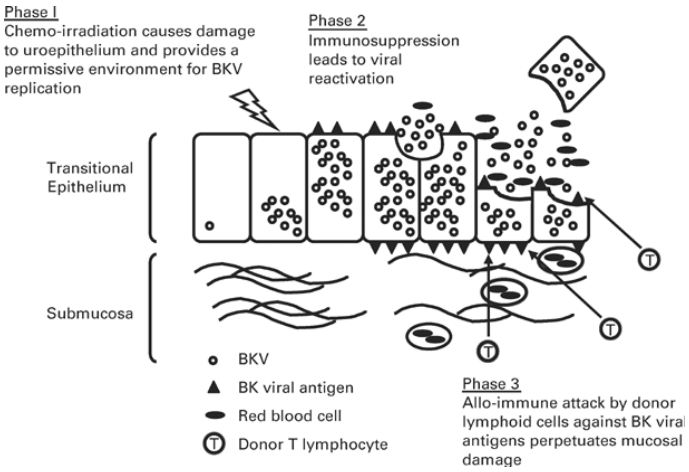
Source: US Renal Data System's *Annual Data Report*, 2010, 2011

PVAN progression, especially to late-stage disease, can often cause deterioration of the kidney graft function. Viruria/viremia often precedes serum creatinine increases by weeks or months. With proof of BK infection, clinicians often reduce immunosuppression when increased serum creatinines and renal injury at biopsy are seen. Late diagnosis or intervention after obvious graft dysfunction significantly decreases likelihood of viral clearance. It is also associated with higher chance of graft loss (30% vs < 10%). Intervention and treatment is often too late and ineffectual in patients with end-stage PVAN. End-stage PVAN can clinically and histologically resemble end-stage renal disease with progressive obliteration of the renal tubules.

Relevance of CMX001's anti-BK virus activity

We think BKV reactivation and GU pathology are highly relevant for the solid organ transplant setting. Chemotherapy and radiation can damage the urinary epithelium, allowing BK virus to begin replicating. The immune suppression allows the virus to reactivate and cause damage to the kidney and bladder.

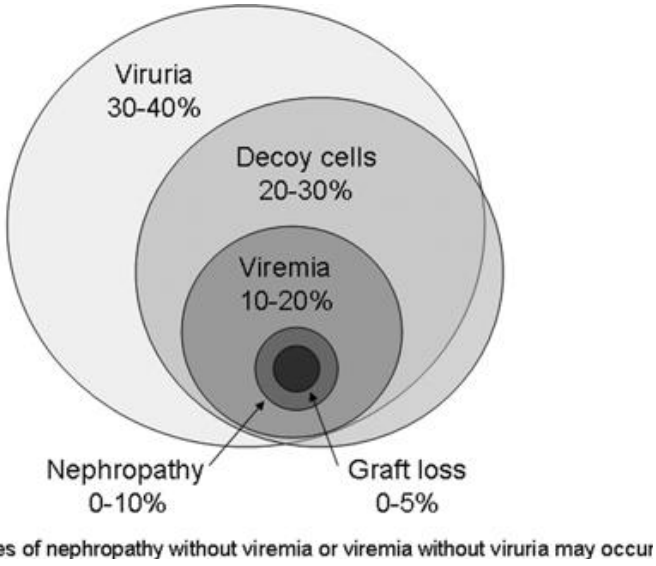
Figure 31: BKV reactivation



Source: Leung, BMT 2005

There are ~16,000 kidney transplants performed each year in the US, according to the National Institute of Diabetes and Digestive and Kidney Diseases, and we think CMRX may be able to unlock this sizeable population if it can show a meaningful reduction in BK virus-related complications such as kidney function.

Figure 32: CMX001's commercial opportunity in kidney transplant patients

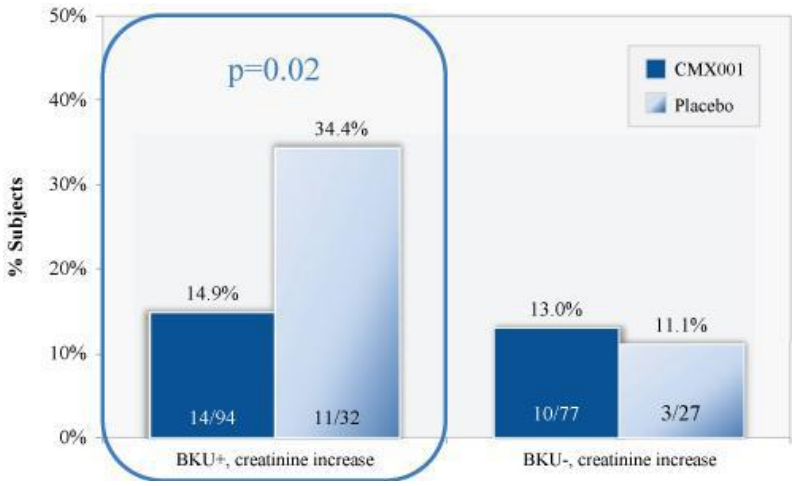


Source: Bohl, CJASN 2007

We think CMX001 has a good potential to show activity on BK virus given its specific beneficial GFR effects. We believe there is a high probability that increases in renal function during the CMRX Phase 2 CMV trial were the result of efficacy against BK PVAN. We see this efficacy as an important differentiating factor for entry into the solid organ

transplant setting and may form the basis for a study of brincidofovir for full approval (CMV indication may be accelerated approval based on SUPPRESS).

Figure 33: CMX001's favorable GFR effect seems specific for patients with BK viruria



Source: Bohl, CJASN 2007

POXVIRUSES

Smallpox is a highly infectious disease of humans with a significant rate of mortality. Smallpox outbreaks have occurred from time to time for thousands of years, but the disease was eradicated after a successful world vaccination program. The last case of smallpox was recorded in the US was in 1949. The last naturally occurring case in the world was in Somalia in 1977. The etiological agent of smallpox is the variola virus. Infection occurs in the upper respiratory tract from oropharyngeal secretions or other viral shedding of an infected individual. Humans are the only natural hosts of variola, and it is not known to be transmitted by insects or animals. Following infection, limited viral replication during the approximately 12-day incubation period produces a primary viremia that infects cells of the reticuloendothilial system. Viral replication in these cells produces a secondary viremia that, following the incubation period, results in an onset of clinical signs and symptoms including fever. During the secondary viremia, macrophage-associated virus is deposited into the capillaries of epithelial tissues where local viral replication and immune response result in lesions in the respiratory tract and in the skin. Oral lesions typically develop 1-2 days after fever with skin lesions following approximately one day later. Death in fatal cases occurs 22-28 days after infection. The cause of death in smallpox has been attributed to toxemia.

Except for laboratory stockpiles, the virus has been eliminated. In the aftermath of the events of September and October 2001, there is a heightened concern that the variola virus may be used as a bioterrorism agent. The US government is therefore taking precautions for dealing with a potential smallpox outbreak.

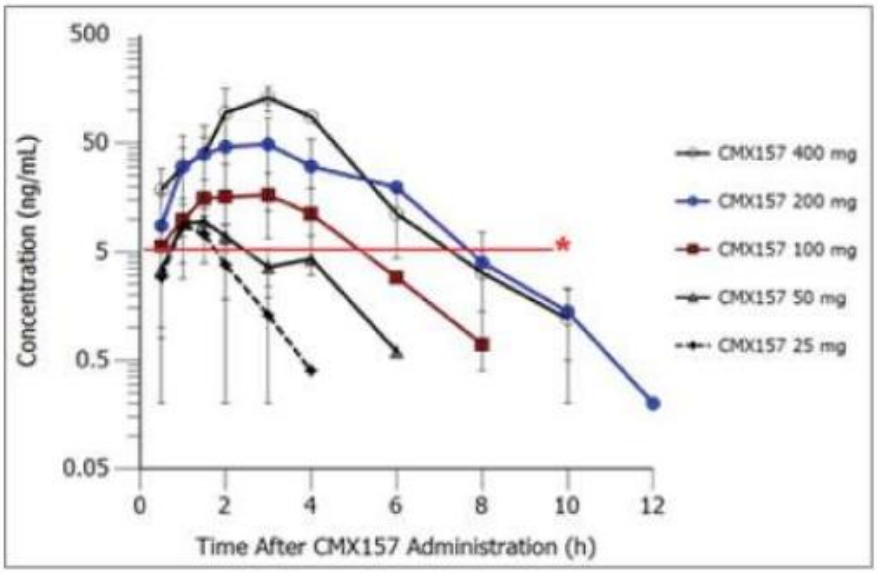
CMX001 is in advanced development for the treatment of smallpox under the "Animal Rule." Because smallpox has been eradicated, the effectiveness of anti-variola (VARV) agents cannot be demonstrated in human clinical trials. CMX001 successfully treated animal pox viruses (similar to variola, and used in clinical trials on animals because variola is carried only by humans). Based on the success of CMX001 on multiple animal models, we believe that CMX001 is a viable treatment for smallpox in the event of its release.

CMX157

CMX157 is Chimerix's second oral nucleotide compound. It uses the same proprietary lipid technology as CMX001 to deliver high intracellular concentrations of tenofovir, another potent antiviral drug. CMX157 is being developed for the treatment of HIV and was licensed to Merck in July 2012. An IND was submitted for the compound for the treatment of HIV on April 30, 2009, but Merck is now the sponsor of this IND.

Tenofovir is the active molecule underlying the prodrug, Viread, which is currently marketed in the US by Gilead. It is most commonly used as a nucleotide reverse transcriptase inhibitor (NRTI) and is approved for the treatment of HIV and chronic hepatitis. Based on preclinical data, CMX157 has the potential for higher intracellular concentrations in target tissues of tenofovir-diphosphate, the active form of CMX157 and Viread. It also offers a decreased frequency of dosing and an improved safety profile over existing NRTIs. CMX157 is 200-fold more potent *in vitro* versus tenofovir against all major HIV subtypes resistant to current therapies. CMX157 allows for decreased circulating levels of tenofovir, thereby lowering systemic exposure and reducing the potential for renal side effects.

Figure 34: Plasma concentrations after oral administrations of CMX 157



*Concentration that equaled TFV-PP level produced by TFV peak concentration *in vitro* .

Source: Company website

A Phase 1 study has been completed in healthy subjects. Favorable safety, tolerability, and drug distribution profiles were shown.

Figure 35: Overview of P1 study for CMX157

Trial	A Safety, Tolerability and Pharmacokinetic Study of a Single Dose of CMX157 in Healthy Volunteers
NTC ID	NCT01080820
Condition	CMV infection
Design	Randomized, Safety/efficacy study, Double blind (subject, investigator), Parallel assignment
Treatment Arms	Placebo + Viread, Viread, CMX157+Viread
Treatment Duration	One single dose
Enrollment	36
Key Entry Data	Males or females of non-childbearing potential, 18 to 55 years of age. Males must be able and willing to use adequate contraceptive methods throughout the study.
Primary endpoints	Adverse events (AEs), absolute values and changes over time of clinical chemistry including troponin, hematology, and urinalysis, vital signs (blood pressure (BP) and heart rate), electrocardiogram [Time Frame: dosing-28 days post-dose] [Designated as safety issue: Yes]
Secondary endpoints	CMX157 PK parameters: AUC(0-∞), AUC(0-t), Cmax, C12, and C24 following single dose administration. [Time Frame: dosing - 28 days post-dose] [Designated as safety issue: No]

Source:clinicaltrials.gov

INTELLECTUAL PROPERTY

Chimerix is not aware of any third-party patents (other than those licensed by CMRX) encompassing propriety compounds CMX001 and CMX157. The company has the rights to the development and commercializing of lipid antiviral conjugates CMX001 and CMX157 and derivatives of the two compounds. The company plans to file patent applications directed to dosage forms, methods of treatment, and identification of additional nucleoside phosphonate compounds and their derivatives in order to protect their lipid-antiviral conjugate therapeutics and maintain their unique position in the antiviral field. The Hatch-Waxman act may extend one of the CMX001 and one of the CMX157 patents for five years. Patents for the compounds expire between 2020 and 2031 internationally. The company is also expanding its intellectual property estate into the area of novel anti-fungal nucleoside phosphonates. Chimerix also has a chemical library of over 10,000 heterocyclic compounds purchased from the University of Michigan, of which there are approximately 3,500 nucleoside analog candidates for lipid conjugation. Chimerix is currently investigating compounds in the library and has identified viable hits against pathogens including influenza, clinically important fungi, and CMV and BKV. Selection is in progress for the antifungal and dual active CMV/BKV compounds. Chimerix will owe royalties to the University of Michigan for any of the compounds that yield commercial success.

Figure 36: Summary of CMRX key patents

Patent	Title	Expiration
6,716,825	Composition of matter (CMX001)	2020
7,034,014	Composition of matter (CMX001)	2020
7,094,772	Composition of matter (CMX001)	2020
7,790,703	Composition of matter (CMX001)	2020
6,716,825	Method of use (CMX001)	2020
7,452,898	Method of use (CMX001)	2020
7,790,703	Method of use (CMX001)	2020
6,716,825	Composition of matter (CMX 157)	2020
7,034,014	Composition of matter (CMX 157)	2020
7,094,772	Composition of matter (CMX 157)	2020
7,790,703	Composition of matter (CMX 157)	2020
7,687,480	Composition of matter (CMX 157)	2020
6,716,825	Method of use (CMX157)	2020
7,790,703	Method of use (CMX157)	2020
7,687,480	Method of use (CMX157)	2020
7,944,143	Nucleoside phosphonate antiviral compound	2027-2028
7,749,983	Nucleoside phosphonate antiviral compound	2027-2028

Source: Company reports and Canaccord Genuity estimates

MANAGEMENT TEAM

The Chimerix management team has a strong history of corporate leadership, development and commercialization in the biotechnology industry.

Kenneth Moch joined Chimerix in 2009 as the chief operating officer and was named president and CEO in April 2010. He has more than 30 years of experience in the biomedical arena. He founded Euclidian Life Science Advisors, where he was most recently the president and CEO of BioMedical Enterprises, Inc. He also co-founded The Liposome Company. He served as managing director of Healthcare Investment Banking at ThinkEquity Partners and was the president and CEO of Alteon, Inc. He pioneered the storage and therapeutic use of cord blood stem cells and launched the first cord blood stem cell bank as the president and CEO of Biocyte Corporation. He is currently a member of the Board of Directors of M2Gen.

Chimerix's SVP and CFO, Timothy Trost, officially joined Chimerix in 2011 but has been working with the company since 2010 in a consulting capacity. He has over 30 years of experience in the financial field, and has served as vice president and CFO at Argos Therapeutics, Inc. He was the SVP and CFO at InteCardia, Inc., and played a key role in negotiating and executing the sale of the company to Syncor International Corporation. He also served as executive vice president and CFO of Coastal Physician Group, Inc., and was the VP of Finance at Morganite North America. He began his professional career at PricewaterhouseCoopers LLP, where he spent time in four offices over 12 years.

In 2012, Dr. Michelle Berrey joined Chimerix as the chief medical officer. Prior to joining Chimerix, she was the chief medical officer at Pharmasset from 2007 until its acquisition by Gilead Sciences in January 2012. Dr. Berrey has significant expertise in the design, early development, medical governance, clinical strategy and product life cycle management of antiviral compounds. Dr. Berrey has also served as vice president, viral diseases, clinical pharmacology & discovery medicine at GlaxoSmithKline, where she was responsible for the early development of compounds for the treatment of HIV, hepatitis viruses, and hepatic fibrosis.

Ms. Linda M. Richardson joined CMRX in December 2013 from Sanofi, where she most recently served as vice president and head of the global lixisenatide franchise, leading the commercial worldwide launch of Lyxumia, a new injectable drug for Type 2 diabetes. While at Sanofi, she also led the pre-launch strategy development for several other products, and reinvigorated Multaq performance in the U.S. Prior to joining Sanofi, Ms. Richardson was vice president of marketing at Reliant Pharmaceuticals, where she directed the marketing and market research functions for the cardiovascular portfolio. She was instrumental in building and implementing the successful launch of the first prescription omega-3 product, which helped lead to the company's acquisition by GlaxoSmithKline. Ms. Richardson held various positions of increasing responsibility at GlaxoSmithKline in the sales, market research, and marketing functions. Ms. Richardson served on the Board of Directors of Healthy Women, a non-profit organization dedicated to promoting health and wellness among women. She earned her BA in English at the University of Pennsylvania.

Dr. Michael D. Rogers has served as CMRX's chief development officer since March 2013. From 2007 to 2012, Dr. Rogers served as chief development officer at Pharmasset, Inc., where his primary responsibility was to facilitate the design and implementation of development programs for HCV antiviral compounds. From 2004 to 2007, Dr. Rogers served as vice president, Division of Viral Diseases at GlaxoSmithKline, where he was responsible for antiviral discovery activities directed toward HIV and hepatitis C virus indications. From 2001 to 2004, Dr. Rogers served as vice president, antiviral discovery medicine at GlaxoSmithKline. Dr. Rogers has over 29 years of industry experience and has participated in all phases of antiviral and anti-infective drug development, including discovery, preclinical development, and phase 1, 2, 3, and 3b/4 clinical development programs. Dr. Rogers received his doctorate in medical parasitology and a master of public health degree in medical microbiology from the University of North Carolina, Chapel Hill. He completed a postdoctoral fellowship in clinical microbiology at St. Jude Children's Research Hospital in Memphis, Tennessee.

Dr. Hervé Mommeja-Marin has served as the vice president, clinical research of CMRX since July 2010. From September 2006 to June 2010, Dr. Mommeja-Marin served as senior medical director, infectious diseases, for i3 Research Limited, a contract research organization, where he was the lead therapeutic expert in infectious diseases. From June 2005 to September 2006, Dr. Mommeja-Marin served in various roles, most recently as director of clinical research at Gilead Sciences, Inc., where he was responsible for the global development of hepatitis B and hepatitis C programs. Dr. Mommeja-Marin received a medical degree from Paris VII University, France. Dr. Mommeja-Marin received his French certifications in internal medicine and multiple subspecialties.

Figure 37: CMRX key management members

Name	Title	Work history	Joined CMRX in:
Kenneth I. Moch	President, CEO and Director	Euclidian Life Science Advisors Alteon The Liposome Company	2009
Timothy W. Trost	SVP, CFO and Corporate Secretary	Argos Therapeutics InteCardia PricewaterhouseCoopers	2010
M. Michelle Berrey, M.D., M.P.H.	Chief Medical Officer	Pharmasset GlaxoSmithKline	2012
Linda M. Richardson	Chief Commercial Officer	Sanofi Reliant Pharmaceuticals GlaxoSmithKline	2013
Michael D. Rogers, Ph.D.	Chief Development Officer	Pharmasset GlaxoSmithKline	2013
Hervé Momméja-Marin, M.D.	Vice President, Clinical Research	i3 Research, a UnitedHealth Group Company Gilead Sciences Triangle Pharmaceuticals	2010

Source: Company reports and Canaccord Genuity estimates

Figure 38: CMRX P&L

	2011A	2012A	Q1/13A	Q2/13A	Q3/13A	Q4/13E	2013E	Q1/14E	Q2/14E	Q3/14E	Q4/14E	2014E	2015E
CMX001 US revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
CMX157 royalties													
Product revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Collaboration and licensing revenue	0.1	17.5	-										
Contract and grant revenue	12.0	16.3	1.8	0.8	0.9	1.3	4.7	0.7	0.7	0.7	0.7	2.6	80.0
Total revenues	**12.1**	**33.7**	**1.8**	**0.8**	**0.9**	**1.3**	**4.7**	**0.7**	**0.7**	**0.7**	**0.7**	**2.6**	**80.0**
Cost of goods sold		-	-	-	-	-	-	-	-	-	-		
Gross Profit	**12.1**	**33.7**	**1.8**	**0.8**	**0.9**	**1.3**	**4.7**	**0.65**	**0.65**	**0.65**	**0.65**	**2.6**	**80.0**
R&D expense	27.7	27.8	6.5	6.3	5.3	10.5	28.6	10.5	11.0	11.5	12.0	45.0	30.0
SG&A expense	9.4	8.7	1.8	2.2	2.0	2.7	8.7	2.8	3.0	3.1	3.3	12.2	30.0
Other operating expense	-	0.0					-	-	-	-	-	-	-
Total operating expense	**37.1**	**36.5**	**8.3**	**8.5**	**7.3**	**13.2**	**37.3**	**13.3**	**14.0**	**14.6**	**15.3**	**57.2**	**60.0**
Operating income	**(25.0)**	**(2.8)**	**(6.5)**	**(7.7)**	**(6.4)**	**(12.0)**	**(32.6)**	**(12.7)**	**(13.3)**	**(14.0)**	**(14.6)**	**(54.6)**	**20.0**
Net Interest/Investment income	-	-					0.0					0.0	0.0
(interest expense)	(0.2)	(0.8)	(0.4)	(0.4)	0.3	(0.4)	(0.9)	(0.4)	(0.4)	(0.4)	(0.4)	(1.6)	0.1
Fair value adjustment to warrant liability	(0.4)	(0.8)	(2.2)	(4.4)	-	-	-					-	-
Interest and other, Net	(0.6)	(1.6)	-	-	-	-	-	-	-	-	-	-	-
Pre-tax income	**(25.6)**	**(4.4)**	**(9.1)**	**(12.5)**	**(6.7)**	**(12.4)**	**(33.5)**	**(13.1)**	**(13.7)**	**(14.4)**	**(15.0)**	**(56.2)**	**20.1**
Accretion of redeemable convertible preferred stock	9.6	4.4	25.5	8.6	-	-	34.1					-	-
Net income (loss)	**(35.2)**	**(8.8)**	**(34.6)**	**(21.0)**	**(6.7)**	**(12.4)**	**(67.6)**	**(13.1)**	**(13.7)**	**(14.4)**	**(15.0)**	**(56.2)**	**20.1**
Basic EPS	**(23.20)**	**(5.72)**	**(22.58)**	**(0.91)**	**(0.26)**	**(0.48)**	**(3.55)**	**(0.50)**	**(0.52)**	**(0.55)**	**(0.57)**	**(2.14)**	**0.76**
Diluted EPS	**(23.20)**	**(5.72)**	**(22.58)**	**(0.91)**	**(0.26)**	**(0.48)**	**(3.55)**	**(0.50)**	**(0.52)**	**(0.55)**	**(0.57)**	**(2.14)**	**0.76**
Basic shares outstanding	1.5	1.5	1.5	23.0	25.8	25.9	19.1	26.0	26.2	26.3	26.4	26.2	26.4
Diluted shares outstanding	1.5	1.5	1.5	23.0	25.8	25.9	19.1	26.0	26.2	26.3	26.4	26.2	26.4

Source: Company reports and Canaccord Genuity estimate

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	990	100.0%	

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