

ContraVir Pharmaceuticals, Inc. (CTRV - NASDAQ)

CTRV: Initiating Coverage – FV-100 a Potential Game Changer for the treatment of shingles and the prevention of PHN.

INITIATION

We are initiating coverage of ContraVir Pharmaceuticals, Inc. with an Outperform rating and \$6.00 price target. The company's lead compound, FV-100, has completed a Phase 2 trial in which the drug demonstrated the potential to prevent the onset of post-herpetic neuralgia (PHN), a debilitating neuropathic pain syndrome that is the most common complication of herpes zoster, commonly referred to as shingles. In addition, the company has in-licensed CMX-157, a lipid conjugate of the leading antiviral medication tenofovir that is currently used to treat hepatitis B (HBV) and human immunodeficiency virus (HIV).

ContraVir recently raised \$9.8 million to initiate the Phase 3 FV-100 clinical trial, with the Phase 2 trial of CMX-157 scheduled to start later in 2015.

Current Recommendation	Outperform
Prior Recommendation	N/A
Date of Last Change	03/09/2015
Current Price (03/09/15)	\$4.61
Target Price	\$6.00

SUMMARY DATA

52-Week High	\$4.94
52-Week Low	\$2.45
One-Year Return (%)	N/A
Beta	N/A
Average Daily Volume (sh)	37,075

Shares Outstanding (mil)	22
Market Capitalization (\$mil)	\$103
Short Interest Ratio (days)	N/A
Institutional Ownership (%)	0
Insider Ownership (%)	N/A

Annual Cash Dividend	\$0.00
Dividend Yield (%)	0.00

5-Yr. Historical Growth Rates	
Sales (%)	N/A
Earnings Per Share (%)	N/A
Dividend (%)	N/A

P/E using TTM EPS	N/A
P/E using 2015 Estimate	N/A
P/E using 2016 Estimate	N/A

Risk Level	Above Average
Type of Stock	Small-Growth
Industry	Med-Biomed/Gene

ZACKS ESTIMATES

Revenue

(In millions of \$)

	Q1 (Sep)	Q2 (Dec)	Q3 (Mar)	Q4 (Jun)	Year (Jun)
2014	0 A	0 A	0 A	0 A	0 A
2015	0 A	0 A	0 E	0 E	0 E
2016					0 E
2017					0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Sep)	Q2 (Dec)	Q3 (Mar)	Q4 (Jun)	Year (Jun)
2014	-\$0.02 A	-\$0.02 A	-\$0.63 A	\$0.30 A	-\$0.41 A
2015	-\$0.07 A	-\$0.36 A	-\$0.14 E	-\$0.12 E	-\$0.68 E
2016					-\$0.28 E
2017					-\$0.25 E

WHAT'S NEW

Initiating Coverage



We are initiating coverage of ContraVir Pharmaceuticals, Inc. (NASDAQ: CTRV) with an Outperform rating and a \$6.00 price target. ContraVir is developing FV-100, an orally available, small molecule nucleoside analogue prodrug for the treatment of herpes zoster, commonly referred to as shingles, which is an infection caused by the reactivation of the varicella zoster virus (VZV). The company is focused on the development of FV-100 for the prevention of post-herpetic neuralgia (PHN), a debilitating neuropathic pain syndrome that is the most common complication of shingles.

Preclinical studies show that FV-100 is much more potent against VZV compared to acyclovir, valacyclovir, and famciclovir, the currently available FDA approved compounds utilized to treat shingles. Antiviral activity experiments further demonstrate that FV-100 has a more rapid onset of antiviral activity and may work at much lower concentrations. Lastly, pharmacokinetic data from completed Phase 1 and 2 clinical trials indicate that FV-100 has the potential for once or twice daily oral dosing, compared to the three to five times a day dosing necessary for the currently approved therapeutics.

FV-100 was tested in a Phase 2 clinical trial that concluded in December 2010. This trial was the first evaluation of FV-100 in shingles patients, and tested two different doses of FV-100 compared to an active control dose of valacyclovir (Glaxo's Valtrex®). A total of 350 patients aged 50 years and older were enrolled in the three treatment arms: 200 mg FV-100 administered once daily, 400 mg FV-100 administered once daily, and 1,000 mg valacyclovir administered three times per day. Along with evaluating safety and tolerability, the trial examined the effects of FV-100 in reducing the severity and duration of shingles-related pain, the time to lesion healing, and the incidence of PHN.

Results show that FV-100 was generally safe and well tolerated. In addition, there was a clear reduction in the incidence of PHN as 20.2% of those treated with valacyclovir developed PHN compared to 12.4% of those treated with 400 mg FV-100. PHN is the paramount concern for physicians and patients treating a shingles outbreak. Onset of PHN also entails the use of additional pain medications, including opioids, added cost, and potential complications. While the study was not powered to show a statistically significant difference, a 37% relative reduction in the risk of PHN for patients taking 400 mg FV-100 is likely a clinically meaningful result.

In December 2014, ContraVir in-licensed CMX157 from Chimerix, Inc. (Nasdaq: CMRX). CMX157 is a prodrug of tenofovir, a nucleotide analog inhibitor of reverse transcriptase that is currently approved for the treatment of human immune deficiency virus (HIV) and chronic hepatitis B infection sold by Gilead Sciences (Nasdaq: GILD) as Viread®. Chimerix utilized a proprietary technology to covalently modify CMX157 with a lipid side-chain that mimics a naturally occurring phospholipid component of cell membranes. The lipid-conjugated molecule can then utilize natural uptake pathways to achieve oral bioavailability, enhance uptake into cells, avoid many toxicities, and yield higher intracellular concentrations of drug. ContraVir is currently developing a clinical plan for CMX157 with plans to initiate a Phase 2 clinical trial in hepatitis B patients within the next 12-18 months.

As of December 31, 2014 the company had \$8.8 million in cash due to a series of private placements of shares of Series A Preferred Stock to a non-U.S. investor. These funds are being utilized to initiate the Phase 3 clinical trial of FV-100 and the Phase 2 trial of CMX157.

INVESTMENT THESIS

Varicella-Zoster Virus

The varicella-zoster virus (VZV) is a human alphaherpesvirus that causes varicella (chickenpox) and herpes zoster (shingles). Before the advent of a vaccine, chickenpox was a common childhood illness associated with fever and a generalized pruritic vesicular rash. As is common with all alphaherpesviruses, which includes herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), VZV is capable of establishing lifelong latent infection in the cells of the peripheral nervous system after the initial infection ([Weller, 2011](#)). For reasons that are not yet fully understood, some individuals with a previous primary VZV infection will go on to develop shingles. There is no seasonal pattern associated with the development of shingles, thus indicating that the condition arises from reactivation of the latent virus as opposed to new exposures to VZV ([Arvin, 1996](#)). This also indicates that shingles is generally not spread from one individual to another, and only those individuals who have had chickenpox are at risk for developing shingles.

...Background On Shingles...

Patients with shingles typically have a unilateral radicular pain (a type of pain that radiates into the lower extremities directly along the course of a spinal nerve root) and a vesicular rash that is usually limited to a single dermatome (an area of the skin that is supplied by a single spinal nerve).



Patient with shingles. Source: www.medicinenet.com

Over 90% of adults in the U.S. have serological evidence for VZV infection, thus putting them at risk for developing shingles ([Choo *et al.*, 1995](#)). The incidence of shingles in the U.S. has increased from approximately 3.2 per 1,000 persons in the 1990's to an estimated 10.0 per 1,000 persons age 22 years and older in 2010 ([Yawn, *et al.*, 2013](#)). Advanced age appears to be a key risk factor for developing shingles, with the incidence rising from 1.6 per 1,000 persons in those ages 20-29 to 12.0 per 1,000 persons in those over 80 years of age. Immunosuppression is another risk factor, whether resulting from cancer or immunosuppressive treatments. Recent epidemiological studies show that the incidence of shingles is increasing, due in part to the aging of the population of many industrialized countries along with the increased use of immunosuppressive agents and an increase of immunocompromised individuals due to cancer therapy.

Nonspecific initial symptoms of shingles include headache, sensitivity to light, and malaise ([Gnann *et al.*, 2002](#)). Occasionally, the patient may notice pain before the appearance of lesions; however, the first recognizable symptom of shingles is usually the development of lesions that continue to form for up to a week and evolve through stages of postulation, ulceration, and crusting. The lesions typically occur on the torso along the path of nerves that emanate from the spinal cord, however lesions can also be found along the face, neck, and lower back.

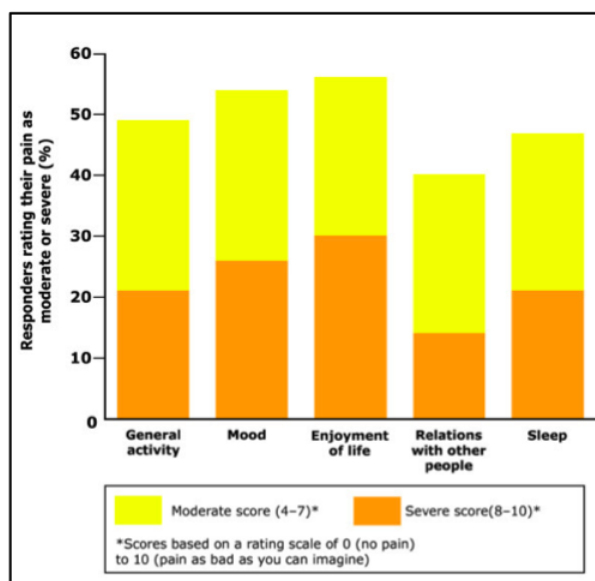
The pain associated with shingles is typically reported to be a deep aching or burning along with altered sensitivity to touch, exaggerated response to stimuli, or electric shock-like pains. Most patients will experience some form of pain for a few weeks. A majority of patients will experience further pain that lasts from anywhere from one to three months. For approximately 15-20% of patients the pain is persistent for more than three months, at which point it is referred to as post-herpetic neuralgia (PHN).

Type	Time Frame	% of patients
Prodromal	Prior to rash	
Acute	2-4 weeks	~90%
Subacute/Chronic	30-90 days	>50%
Post-herpetic neuralgia (PHN)	>90 days	15-20%

Source: ContraVir Pharmaceuticals, Inc.

...Post-Herpetic Neuralgia...

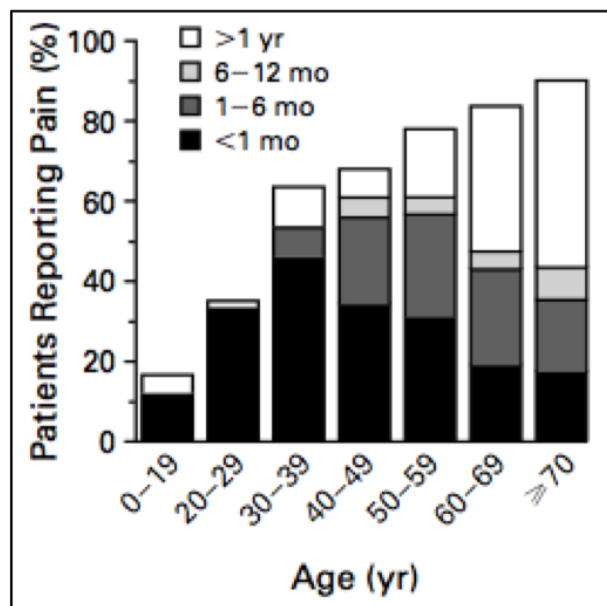
PHN is one of a number of types of neuropathic pain (NP), which is a chronic pain caused by tissue damage or disease that affects the somatosensory system, which is the part of the sensory system associated with the conscious perception of touch, pressure, pain, temperature, position, movement, and vibration. The pain associated with PHN can be severe and debilitating and in many patients it has a negative impact on the quality of life by affecting mood, sleep, and overall well-being ([Magrinelli et al., 2013](#); [Johnson et al., 2010](#)). This is depicted in the following figure, which shows the percentage of PHN patients who reported how pain moderately or severely affected the different aspects of their lives.



Source: Johnson et al., 2010

In some patients, pain and temperature detection systems are hypersensitive to light mechanical stimulation (allodynia). Other patients may have severe and spontaneous pain with no allodynia. Since pain is unique to each individual, the words that describe PHN vary considerably and include pricking, tingling, burning, stabbing, or aching. While the exact mechanism is unclear, the pain appears to result from injury of the peripheral nerves brought about by the virus and the associated inflammatory response.

The incidence and the duration of PHN following shingles are directly correlated with the patient's age, with each one-year increment in age associated with nine and 12 percent increases in the prevalence of PHN at 30 and 60 days post infection, respectively ([Choo et al., 1997](#)). The following chart shows the increase in length of time that pain is present in older shingles patients.



Source: Kost *et al.*, 1996

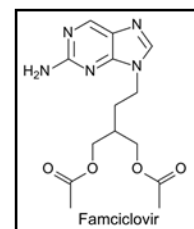
The type of pain along with the variability of its duration makes PHN a very difficult condition to properly treat, and suggests that multiple pathophysiological mechanisms are likely to be involved in its manifestation. Numerous medications have been evaluated in clinical trials to treat PHN, including gabapentin (Neurontin®, Gralise®), pregabalin (Lyrica®), topical lidocaine, topical capsaicin, and gabapentin enacarbil (Horizant®), each of which has received FDA approval for the PHN indication. In addition, the American Academy of Neurology also recommends tricyclic antidepressants and opioids as first-line treatments for PHN.

Pain associated with PHN is often refractory to treatment and many patients require more than one agent to achieve significant pain relief. Also, approximately 40-50% of patients with PHN do not respond to any treatment, with other patients experiencing limited efficacy. Thus, given the difficulty in treating PHN, the ability to prevent or limit the onset of PHN would offer a unique treatment option for shingles patients.

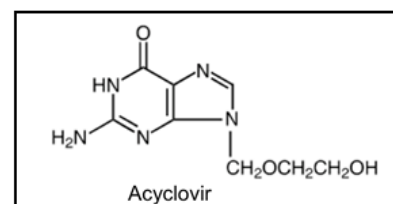
...Current Treatment Options for VZV...

There are currently three antiviral therapies approved by the FDA for the treatment of shingles: famciclovir, acyclovir, and valacyclovir.

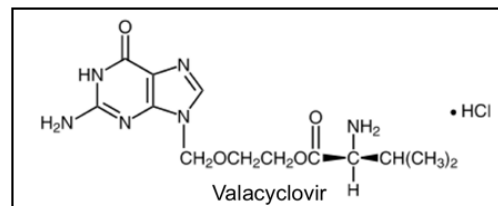
Famciclovir (Famvir®): Famciclovir, a prodrug of penciclovir, is a guanosine analog that has antiviral activity against HSV-1, HSV-2, and VZV due to its high affinity for viral thymidine kinase, which converts famciclovir to famciclovir monophosphate. Additional cellular enzymes convert famciclovir monophosphate to famciclovir triphosphate, which in turn inhibits replication of viral DNA by: 1) inhibiting viral DNA polymerase; 2) incorporation into and termination of the elongating DNA strand; and 3) inactivation of the viral DNA polymerase. Clinical trials of famciclovir showed it reduced the duration of viral shedding, limited the duration of new lesion formation, and accelerated healing (Tyring *et al.*, 1995). In addition, a subgroup analysis showed that in patients >50 years of age who had persistent pain after skin healing, the duration of PHN in famciclovir treated patients was 63 days compared to 163 days in the placebo group. For the treatment of shingles, famciclovir is dosed at 800 mg three times a day for seven days.



Acyclovir (Zovirax®): Acyclovir is a synthetic purine nucleoside analog that has a similar mechanism of action as famciclovir, in that it inhibits viral DNA replication through interactions with viral DNA polymerase. Clinical trials of acyclovir showed that in shingles patients the drug shortened the time to lesion scabbing, healing and pain; reduced the formation of new lesions; and reduced the prevalence of localized, shingles-associated neurologic symptoms (Huff *et al.*, 1988). For the treatment of shingles, acyclovir is dosed at 800 mg five times a day for seven to 10 days.



Valacyclovir (Valtrex®): Valacyclovir is the *L*-valyl ester of acyclovir that is rapidly converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism. Administration of valacyclovir results in serum levels of acyclovir three to five times higher than with oral acyclovir dosing. A clinical trial showed that patients dosed with acyclovir or valacyclovir resulted in equivalent rates of cutaneous healing (Beutner *et al.*, 1995). In addition, valacyclovir significantly shortened the median time to the resolution of shingles-associated pain in comparison to acyclovir (38 days vs. 51 days, $P = 0.001$). For the treatment of shingles, valacyclovir is dosed at 1000 mg three times a day for seven days.



Each of the antiviral therapies is available as a generic. Based upon data collected by ContraVir, there were approximately 17 million prescriptions for famciclovir, acyclovir, and valacyclovir in 2009, with approximately 15-30% of those written for the treatment of shingles. Glaxo sold roughly \$1.75 billion in Valtrex® sales at its peak in 2009. The majority of Valtrex® sales in 2009 were in HSV, but the aforementioned estimate of 15-30% in shingles equates to sales in the \$260 to \$520 million range.

...Drawbacks to Currently Approved Antivirals...

Clinical trials of the aforementioned antiviral therapies have shown them to be successful in lessening the dermatological symptoms of shingles patients when treatment begins within 72 hours of the first appearance of a shingles-related rash or lesion. However, there are a number of drawbacks with the currently available antivirals, such as:

- ✓ None are approved for the reduction of shingles-associated pain or prevention of PHN. While past clinical trials have shown that antiviral therapy reduces the duration of pain, none of the antivirals is approved for the reduction of shingles associated pain or the prevention of PHN.
- ✓ Inconvenient dosing. Each of the approved shingles medications must be taken multiple times per day: Famciclovir – three times per day; Acyclovir – five times per day; Valacyclovir – three times per day. There are multiple studies that have examined the relationship between dosing frequency and patient compliance, as medication non-adherence can lead to suboptimal health outcomes. Claxton *et al.* showed a statistically significant difference in compliance between once-daily (QD) and three-times-daily (TID) medications (79% vs. 65%, $P = 0.008$).
- ✓ Current antiviral dosages must be adjusted for patients with renal insufficiency. Although the currently available antiviral medications are generally safe and well tolerated, dosing must be adjusted for patients who have renal insufficiency to avoid potential adverse events.

...Shingles Vaccines...

Zostavax® is a vaccine developed by Merck (NYSE: MRK) for the prevention of shingles. It contains a minimum of 19,400 plaque-forming units of live/attenuated VZV (Oka/Merck strain) that is administered subcutaneously in the upper arm. The vaccine is approved for those age 50 and greater, however the Centers for Disease Control (CDC) only recommends the vaccine for all those 60 years of age and older, with no specific recommendation for those age 50-59. This is due to the fact that there is no long-term data on the effectiveness of the vaccine beyond four years.

Two different clinical trials (ZEST and SPS) examined the efficacy of Zostavax®. The ZEST trial enrolled 22,439 subjects between the ages of 50-59 to receive a single dose of Zostavax® ($n = 11,211$) or placebo ($n = 11,228$). The subjects were followed for an average of 1.2 years. The results of the ZEST trial showed that compared to placebo, Zostavax® significantly reduced the risk of developing shingles by 69.8%.

The SPS trial enrolled 38,546 individuals age 60 years and older to receive a single dose of Zostavax® ($n = 19,270$) or placebo ($n = 19,276$) (Oxman *et al.*, 2005). The subjects were followed for an average of 3.1 years. The following table gives the results of the SPS trial both overall as well as stratified by age. Zostavax® significantly reduced the risk of developing shingles, with vaccine efficacy highest in those subjects 60-69 years of age.

Age group [†] (yrs.)	ZOSTAVAX			Placebo			Vaccine Efficacy (95% CI)
	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	# subjects	# HZ cases	Incidence rate of HZ per 1000 person-yrs.	
Overall	19254	315	5.4	19247	642	11.1	51% (44%, 58%)
60-69	10370	122	3.9	10356	334	10.8	64% (56%, 71%)
70-79	7621	156	6.7	7559	261	11.4	41% (28%, 52%)
≥80	1263	37	9.9	1332	47	12.2	18% (-29%, 48%)

* The analysis was performed on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.

[†] Age strata at randomization were 60-69 and ≥70 years of age.

Source: Zostavax® prescribing information

An additional analysis performed for the SPS trial was the development of shingles-related complications in those subjects that developed shingles. The following table shows the rate of PHN in evaluable shingles cases. Vaccination with Zostavax® reduced the incidence of PHN in those patients 70 years of age and older; however, it did not affect the incidence of PHN in patients age 60-69.

Age group (yrs.) [†]	ZOSTAVAX					Placebo					Vaccine efficacy against PHN in subjects who develop HZ postvaccination (95% CI)
	# subjects	# HZ cases	# PHN cases	Incidence rate of PHN per 1,000 person-yrs.	% HZ cases with PHN	# subjects	# HZ cases	# PHN cases	Incidence rate of PHN per 1,000 person-yrs.	% HZ cases with PHN	
Overall	19254	315	27	0.5	8.6%	19247	642	80	1.4	12.5%	39% [§] (7%, 59%)
60-69	10370	122	8	0.3	6.6%	10356	334	23	0.7	6.9%	5% (-107%, 56%)
70-79	7621	156	12	0.5	7.7%	7559	261	45	2.0	17.2%	55% (18%, 76%)
≥80	1263	37	7	1.9	18.9%	1332	47	12	3.1	25.5%	26% (-69%, 68%)

* PHN was defined as HZ-associated pain rated as ≥3 (on a 0-10 scale), persisting or appearing more than 90 days after onset of HZ rash using Zoster Brief Pain Inventory (ZBPI). {3}

[†] The table is based on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.

[‡] Age strata at randomization were 60-69 and ≥70 years of age.

[§] Age-adjusted estimate based on the age strata (60-69 and ≥70 years of age) at randomization.

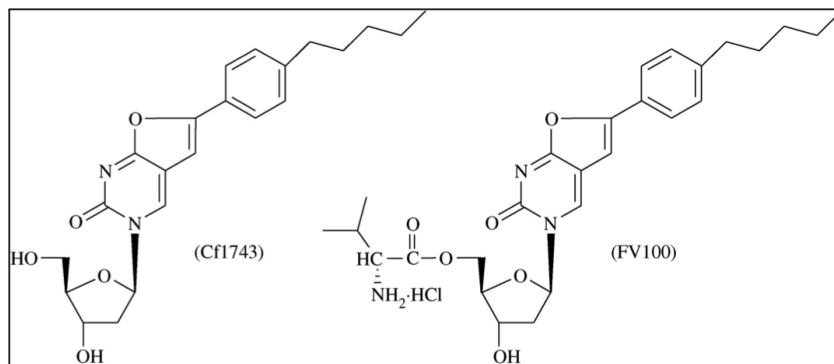
Source: Zostavax® prescribing information

While shown to significantly reduce the incidence of shingles, the fact remains that the vaccine is only 50% effective in patients 60 years of age and older. A 2013 study showed very low uptake for the vaccine initially after it was approved (2007-2009), with only 3.9% of 766,330 randomly selected individuals 65 years of age and older from a Medicare database having received the vaccine ([Langan et al., 2013](#)). However, uptake has likely increased somewhat in recent years as judged by increasing sales of Zostavax®, with Merck reporting \$758 million in 2013 compared to \$332 million in 2011.

While Zostavax® is the only currently approved shingles vaccine, additional shingles vaccines are under development. GlaxoSmithKline (NYSE: GSK) recently [announced](#) that a Phase 3 study of an investigational shingles vaccine reached its primary endpoint. The topline results showed that the vaccine (HZ/su) reduced the risk of shingles by 97.2% compared to placebo in adults aged 50 years and older. The ongoing Phase 3 trial was initiated in 2010 and involves more than 16,000 people in 18 countries. The full data set will be presented at a scientific conference and submitted for publication in a peer-reviewed journal in the coming months.

FV-100

FV-100 is an orally available, small-molecule nucleoside analog of CF-1743 that is under development by ContraVir for the treatment of shingles and the prevention of PHN. Both compounds belong to a group of molecules known as bicyclic nucleoside analogues (BCNAs), and are differentiated from the acyclic purine nucleoside acyclovir and the related compound famciclovir based on their specificity, as acyclovir and famciclovir are significantly more active against HSV than VZV, thus the reason for the higher clinical dosing of acyclovir/famciclovir/valacyclovir for treating shingles.



Source: McGuigan *et al.*, 2009

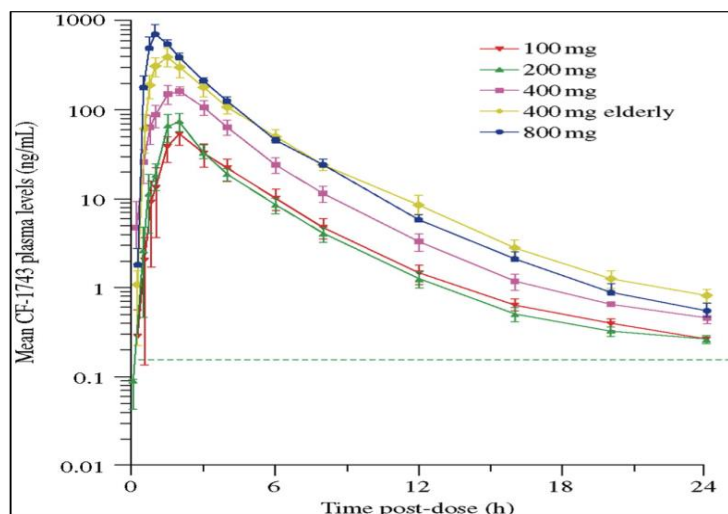
Initial research into BCNAs resulted in compound CF-1743 emerging as the prototype BCNA compound, with early *in vitro* testing showing inhibitor activity against VZV at or below 1 nM, thus being approximately 1,000 times more potent than acyclovir (McGuigan *et al.*, 2000). As with acyclovir/famciclovir, CF-1743 has an absolute requirement for VZV thymidine kinase mediated phosphorylation for antiviral activity; however, unlike acyclovir/famciclovir CF-1743 has virtually no reactivity to HSV thymidine kinase (Sienaaert *et al.*, 2002). One limitation to CF-1743 was a lack of water solubility, which limits oral bioavailability, thus a number of pro-drug formulations were tested to enhance the pharmacokinetic profile of the drug. Just as valacyclovir is the valyl ester form of acyclovir, the valyl ester form of CF-1743 (designated as FV100) was selected for further development based on high solubility, stability, and a favorable pharmacokinetic profile (McGuigan *et al.*, 2007).

...Phase 1 Clinical Studies of FV100...

FV100 was initially evaluated by Inhibitex, Inc. (acquired by Bristol-Myers Squibb in 2012) in three separate Phase 1 clinical trials from 2008 to 2009.

- **Phase 1 Study #1:** A single-ascending dose clinical trial of FV-100 was completed in August 2008. This was a blinded, placebo controlled trial that evaluated the safety and pharmacokinetics of four doses of FV-100 in six cohorts of healthy volunteers (100, 200, 400, and 800 mg, as well as a two 400 mg food effect groups). Each cohort consisted of six subjects that received FV-100 and two that received placebo. There were no serious adverse events observed and the compound was generally well tolerated.
- **Phase 1 Study #2:** In January 2009, a blinded, placebo-controlled trial was completed to evaluate single and multiple doses of FV-100 in healthy subjects 65 years of age and older. One dose cohort consisted of 12 healthy subjects, ten of whom received a single dose of 400 mg of FV-100 and two of whom received placebo, and the second cohort also consisted of 12 healthy subjects, ten of whom received 400 mg of FV-100 administered twice daily for seven consecutive days and two of whom received placebo. The results of this trial demonstrated no significant safety differences between these subjects and those from the multiple ascending dose trial.
- **Phase 1 Study #3:** In February 2009, a blinded, placebo-controlled multiple-ascending-dose study was conducted to evaluate the safety and pharmacokinetics of five oral doses of FV-100 (100, 200, 400 and 800 mg administered once daily and 400 mg administered twice daily, each for seven days) in healthy subjects aged 18 to 55. Each dose cohort consisted of six subjects that received FV-100 and two that received placebo. The results of the trial demonstrated that there were no serious adverse events and FV-100 appeared to be generally well tolerated at all dose levels.

Importantly, as the following graph shows, pharmacokinetic data from the aforementioned studies demonstrated that all doses studied maintained mean plasma levels of CF-1743, the active form of FV-100, above the EC 50 for at least 24 hours, supporting the evaluation of once-daily dosing of FV-100 in future clinical trials. The EC 50, or effective concentration, is shown by the dashed green line in the following chart and represents the concentration of CF-1743 that produces a half maximal response against VZV *in vitro*.



Source: McGuigan et al., 2009

...Phase 2 Clinical Trial of FV-100...

Inhibitex initiated a Phase 2 clinical trial of FV-100 in May 2009 that was completed in December 2010. The trial was a well-controlled, double-blind clinical trial evaluating FV-100 against an active control of valacyclovir. Approximately 350 patients, aged 50 years and older, who had shingles-associated pain and presented to the clinic within 72 hours of the appearance of their first shingles lesion, were randomized to one of three treatment arms: 200 mg FV-100 administered once daily (QD) for seven days, 400 mg FV-100 administered QD for seven days, or 1,000 mg valacyclovir administered three times per day (TID) for seven days.

The primary endpoint of the study was a reduction in herpes zoster associated pain and severity as measured by the Zoster burden of illness (Zoster BOI) scale after 30 days of treatment. The trial was 80% powered to detect an approximate 20-25% difference between the FV-100 and Valtrex® cohorts. Secondary endpoints included the BOI after 90 days, incidence of PHN, mean time to lesion crusting and healing, and use of concomitant pain medications.

The following table shows the treatment outcomes with respect to the shingles-associated pain endpoints.

	FV-100 200mg QD (n=107)	FV-100 400mg QD (n=113)	Valacyclovir 1000mg TID (n=109)
Zoster BOI Day 30	114.49	110.31	117.96
Zoster BOI Day 90	221.53	196.94	229.59
Incidence of PHN	17.8%	12.4%	20.2%

Source: Zacks SCR / Napodano

For FV-100 200 mg QD: The data show a 3% reduction on the BOI-30 primary endpoint and a 4% reduction on the BOI-90 endpoint vs. valacyclovir 1000 mg TID. Patients on FV-100 200 mg also had a 12% reduced incidence of PHN (17.8% vs. 20.2%) vs. valacyclovir.

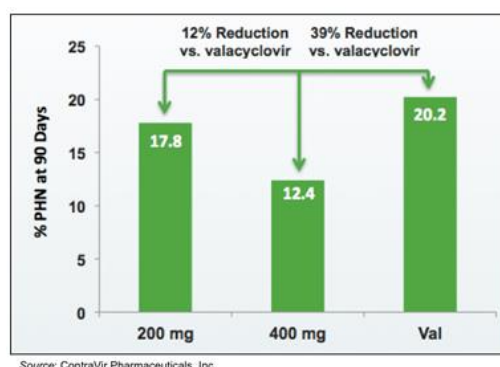
For FV-100 400 mg QD: The data show a 7% reduction on the BOI-30 primary endpoint and a 14% reduction on the BOI-90 endpoint vs. valacyclovir 1000 mg TID. Patients on FV-100 400 mg also had a 37% reduced incidence of PHN (12.4% vs. 20.2%) vs. valacyclovir.

The trial missed the primary endpoint of a 20-25% difference between the FV-100 cohorts vs. Valtrex on the BOI-30 scale. However, there were a number of positives to take away from the trial, including the following:

- ✓ There was continued separation from the FV-100 cohorts and valacyclovir between BOI-30 and BOI-90:
 - FV-100 200 mg QD went from 3% improvement at BOI-30 to 4% improvement at BOI-90
 - FV-100 400 mg QD went from 7% improvement at BOI-30 to 14% improvement at BOI-90

This shows the drug is working over time. Additionally, the average “worst pain” at day 90 was lower for the FV-100 cohorts vs. valacyclovir. The BOI composite endpoint is a measure of both severity and duration. We believe severity clearly trended in FV-100's favor.

- ✓ There is clear dose response, which is a key metric to examine during a Phase 2 proof-of-concept program. The FV-100 400 mg arm showed reduced BOI-30 and BOI-90 scores vs. the FV-100 200 mg arm. This presents the opportunity to test even higher doses in the future.
- ✓ The reduced incidence of PHN is the most clinically meaningful endpoint. PHN is the paramount concern for physicians and patients treating a shingles outbreak. Onset of PHN also entails the use of additional pain medications, including opioids, added cost, and potential complications. While the study was not powered to show a statistically significant difference, a 37% relative reduction in the risk of PHN for patients taking 400 mg FV-100 is likely a clinically meaningful result.



- ✓ Roughly 20% more patients on valacyclovir used opioids (52% vs. 42%) than on FV-100. This is important to note because the BOI-30 and BOI-90 data accounts for pain severity and duration regardless of the use of concomitant pain medications. For FV-100 400 mg the BOI-90 showed a 14% reduction vs. valacyclovir despite the fact that 20% more on valacyclovir were also on opioids.
- ✓ FV-100 offers secondary benefits vs. valacyclovir:
 - FV-100 was once daily (QD) dosing vs. valacyclovir three-times daily (TID) dosing. In addition, the FV-100 400 mg pill is a lot smaller and easier to swallow than the valacyclovir 1000 mg pill.
 - Enrollment characteristics showed that 10% of the patients randomized to the study had baseline creatinine serum levels less than 50 mL/min. The Valtrex® label requires that these patients with potential renal insufficiency receive a lower dose for safety reasons. FV-100 is primarily metabolized by the liver, and thus the FDA is unlikely to require creatinine testing prior to dosing. This could save the physician time and the patient money in the long run.

Safety and tolerability of FV-100 looked similar to valacyclovir. The chart below shows the adverse events (AEs) and serious adverse events (SAEs) as well as discontinuations.

	FV-100 200mg QD (n=117)	FV-100 400mg QD (n=117)	Valacyclovir 1000mg TID (n=116)
Excluded as Zoster Negative	n=10	n=4	n=7
Any Adverse Events	46%	55%	42%
Treatment-Related AEs	21%	26%	20%
Serious Adverse Events	0%	4%	3%
Treatment-Related SAEs	0%	0%	2%

Source: Zacks SCR / Napodano

Adverse events in any cohort that exceeded 10% were headache and nausea. Serious adverse events were low and generally not related to drug treatment. Given the similar safety and tolerability profile of FV-100 vs. valacyclovir, we do not believe there is any limitation that would prohibit use if approved. Given the clear dose response seen in the Phase 2 data, testing a higher dose for the Phase 3 trial may be warranted.

...FV-100 Clinical Plan...

Based upon the Phase 2 results, the company is planning on specifically focusing on the prevention of PHN to differentiate FV-100 from currently available antivirals, as none of them are approved for that indication. The company will be initiating "Clinical Study 007" late in the first quarter or early second quarter of 2015. During the second half of 2014, the company was granted a Type B meeting with the FDA to discuss the proposed design of the trial. The meeting took place early in the first quarter of 2015, with the most important outcome from the meeting being that Study 007 will be regarded as a Phase 3 trial suitable for supporting an NDA filing.

The 007 trial will be a global, multi-center, randomized, double-blind, parallel group, comparative study of FV-100 and valacyclovir at up to 200 centers. The total patient population will be approximately 825 evenly split between three groups: 400 mg FV-100 dosed once a day for seven days, 400 mg FV-100 dosed twice a day for seven days, or 1000 mg valacyclovir dosed three times a day. The patients will be followed for 120 days after treatment.

The primary endpoint will be the difference in incidence of PHN between FV-100 and valacyclovir treated patients. Each day, patients will phone into an interactive voice response system (IVRS) to answer three questions on the zoster brief pain inventory (ZBPI), a questionnaire that measures the impact of the pain and discomfort caused by shingles or PHN on the ability to carry out seven general activities: work, sleep, walking, life enjoyment, mood, relations with others, and general activity (Coplan *et al.*, 2004).

The study subjects will be asked daily:

- 1) Have you had any pain caused by your shingles in the last 24 hours? If they answer "no" they will not be required to answer the next two questions.
- 2) On a scale of 0 to 10, where 0 represents 'no pain' and 10 represents 'pain as bad as you can imagine', what best describes your pain at its worst in the last 24 hours?
- 3) On a scale of 0 to 10, where 0 represents 'no pain' and 10 represents 'pain as bad as you can imagine', what number best describes your pain on the average in the last 24 hours?

The primary efficacy endpoint is the proportion of subjects with PHN at Day 120, and will be determined by Item 3 of the ZBPI, Worst Pain in the Last 24 Hours. PHN will be defined as the average of the ZBPI Worst Pain in the Past 24 Hours scores collected between Days 114 and 120 that is ≥ 3 .

A key secondary endpoint will be time to loss of acute pain, defined as the first occurrence where ZBPI Item 3 (Worst Pain in the Last 24 Hours) as collected daily from the IVRS is equal to 0 and remains at 0 until all the lesions are healed. Additional secondary endpoints include: time to resolution of clinically significant pain (defined as start of the first seven day period where the average of ZBPI Item 3 is < 3 ; time to resolution of pain using ZBPI Item 3; time to resolution of pain after complete lesion healing; time to cessation of new lesion formation; time to complete lesion healing; and changes in pain intensity.

For statistical analysis, it is assumed that no more than 11% of twice-daily FV-100 treated patients and no fewer than 20% of valacyclovir treated patients will experience PHN at Day 120. With 825 total subjects (275 in each group), the trial will be 80% powered to detect the aforementioned difference in incidence of PHN vs. the control, assuming a two-sided 5% significance level.

Antiviral Market Analysis

There are an estimated one million cases of shingles in the U.S. each year (source: NIAID), with approximately 50% of all cases occurring in individuals over the age of 60 and approximately 80% occurring in individuals over the age of 50. The aging population of many Westernized nations means the incidence is expected to continue to increase.

As mentioned previously, none of the antiviral therapies approved for the treatment of shingles are approved for the prevention of PHN. All three antivirals (valacyclovir, acyclovir, famciclovir) are available as generics, with valacyclovir the market leader. In 2012, there were approximately 20 million prescriptions written for valacyclovir (57%), acyclovir (39%), and famciclovir (4%). We estimate that approximately 15% (3 million) of the prescriptions were for shingles patients. According to GoodRx.com, 50 tablets of generic 800 mg acyclovir cost approximately \$75, 21 tablets of generic 1000 mg valacyclovir cost approximately \$225, and 21 tablets of 800 mg famciclovir cost approximately \$50. We estimate Valtrex® sales for shingles in 2009, the year before the patent expiration, totaled roughly \$300 million.

Since all currently available shingles medications are available as generics, in order for ContraVir to justify pricing FV-100 at a premium the results of the Phase 3 study must clearly show a reduction in the risk of developing PHN. We believe a 50% reduction in incidence would be considered clinically meaningful by physicians. The degree of risk reduction will dictate potential pricing and peak revenue opportunity. With 50% risk reduction being the minimum, we estimate peak sales for FV-100 could range anywhere between \$250 and \$700 million.

Hepatitis B Virus

The hepatitis B virus (HBV) is a member of the hepadnavirus family that causes both acute and chronic liver infections. It is estimated that approximately 350-400 million people worldwide have a chronic, lifelong infection. HBV can be classified into 10 genotypes (A to J) based upon an inter-group divergence of more than 8% or more in the complete nucleotide sequence ([Stuyver et al., 2000](#); [Arauz-Ruiz et al., 2002](#); [Olinger et al., 2008](#); [Tatematsu et al., 2009](#)). Recent evidence suggests clinical outcome and response to antiviral therapy may be impacted by HBV genotype.

Acute infection with the hepatitis B virus typically results in a loss of appetite, nausea, vomiting, body aches, mild fever, and jaundice. More than 90% of people infected with the hepatitis B virus will recover and be completely free of the virus within six months. According to the World Health Organization, the likelihood of developing a chronic hepatitis B infection is highly dependent upon the age when the infection occurs ([WHO fact sheet N°204](#)):

- ✓ 80-90% of infants infected during the first year of life develop chronic infections;
- ✓ 30-50% of children infected before the age of six develop chronic infections;
- ✓ Less than 5% of otherwise healthy adults will develop chronic infection;
- ✓ 15-25% of adults who develop chronic infection during childhood will die from hepatitis B associated liver cirrhosis or cancer

Transmission of the virus occurs by exposure to infected blood or bodily fluids, with the most typical modes being sexual contact, blood transfusion, re-use of contaminated syringes, and transmission from mother to child during childbirth.

A vaccine to prevent hepatitis B infection has been available in the U.S. for over 30 years. It is administered as a series of three shots and is now believed to offer indefinite protection against infection ([Van Damme et al., 2007](#)). The vaccine is both safe and effective, with over one billion doses administered worldwide since its introduction, with less than 1% of vaccinated children developing chronic infection.

Tests for the presence of the virus involve screening blood for the presence of viral antigens (proteins produced by the virus) or for antibodies against the virus produced by the host. The hepatitis B surface antigen (HBsAg) is the first detectable antigen to appear in the blood. Shortly thereafter, another viral antigen can be detected in the blood stream (HBeAg). The presence of HBeAg is associated with higher rates of viral replication and infectivity.

...Chronic Hepatitis B Infection...

Chronic HBV infection can be divided into five different phases ([EASL, 2012](#)), which are not necessarily sequential, with each phase necessitating a different treatment protocol:

- 1) **The “immune tolerant” phase:** This phase is characterized by HBeAg positivity, high levels of HBV replication (indicated by high levels of HBV DNA in the blood), normal or low levels of ALT (a liver enzyme that becomes elevated in the bloodstream due to liver injury or disease), mild or no inflammation, and little to no progression of fibrosis. This phase is more frequent and prolonged in those infected perinatally or in the first few years of life.

- 2) The “immune reactive HBeAg-positive” phase: This phase is characterized by HBeAg positivity, lower levels of HBV replication compared to the “immune tolerant” phase, increased or fluctuating levels of ALT, moderate or severe inflammation, and more rapid progression of fibrosis. This phase may occur after several years of the “immune tolerant” phase and may last from several weeks to several years. This phase ends with the seroconversion to anti-HBe (that is, the HBeAg is no longer detectable due to the presence of antibodies to HBe).
- 3) The “inactive HBV carrier” phase: This phase follows seroconversion to anti-HBe and is characterized by very low or undetectable serum HBV DNA levels and normal ALT levels. A minimum follow-up of 1 year while checking ALT levels every 3-4 months, with normal ALT levels the whole time, is required before classifying a patient in this phase. Due to the immunological control of the infection, the “inactive HBV carrier” state carries a favorable long-term outlook with very low risks of cirrhosis or liver cancer ([Tai et al., 2009](#)). HBsAg loss and seroconversion to anti-HBs antibody may occur spontaneously in 1–3% of cases per year, usually after several years with persistently undetectable HBV DNA ([Martinot-Peignoux et al., 2002](#)). However, progression to HBeAg-negative chronic HBV may also occur.
- 4) “HBeAg-negative chronic HBV” phase: This phase follows seroconversion from HBeAg positive to anti-HBe and represents a later immune reactive phase in the natural history of chronic HBV infection. It is characterized by periodic reactivation with a pattern of fluctuating levels of HBV DNA and ALT and active hepatitis ([Hadziyannis et al., 2006](#)). Patients who are HBeAg negative harbor HBV virions who no longer express HBeAg, thus making it difficult to distinguish them from true inactive HBV carriers. However, this distinction is important as inactive HBV carriers have a favorable prognosis, while HBeAg-negative chronic HBV patients have active disease with a high risk of progression to cirrhosis or liver cancer.
- 5) “HBsAg-negative” phase: This phase is characterized by no detectable levels of HBsAg in the blood and the presence of anti-HBc antibodies with or without the presence of anti-HBs antibodies. HBsAg loss before the onset of cirrhosis is associated with a favorable outcome and a decreased risk of developing cirrhosis and/or liver cancer. If cirrhosis develops before the loss of HBsAg, then the patient remains at an increased risk of liver cancer.

...Treatment of Chronic HBV Infection...

The goal of treating chronic HBV infection is to prevent progression of the disease to cirrhosis, end-stage liver disease, liver cancer (hepatocellular carcinoma or HCC), and death. This can usually be achieved by suppressing HBV replication in a sustained manner. However, chronic HBV infection can never be completely eradicated due to the presence of HBV DNA in the nucleus of hepatocytes ([Bréchet et al., 1981](#)) as well integration of the HBV genome into the host genome ([Bréchet, 2004](#)).

Two different types of drugs are utilized in the treatment of chronic HBV infection: conventional or pegylated interferon alpha (INF or PEG-INF) and nucleoside/nucleotide analogs (NAs). Treatment is typically the same regardless of HBeAg status and is dependent upon: serum HBV DNA levels, serum ALT levels, and severity of liver disease.

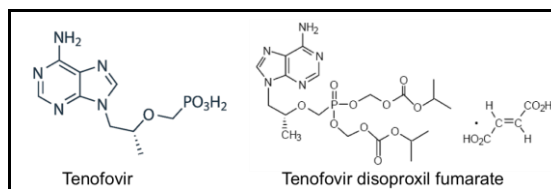
NAs available for the treatment of chronic HBV infection include:

- Nucleoside analogs: lamivudine, telbivudine, emtricitabine, entecavir
- Nucleotide analogs: adefovir and tenofovir

NAs are quite effective at inhibiting HBV replication; however, these treatments are not curative and require life-long dosing with a high risk of developing drug resistance and toxicity ([Scaglione et al., 2012](#)).

...Tenofovir...

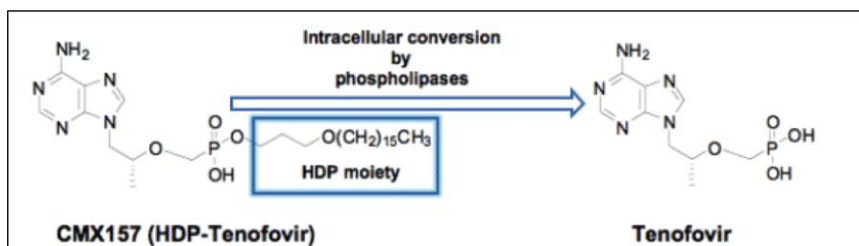
Tenofovir is an NA inhibitor of reverse transcriptase, an enzyme involved in a number of diverse roles during different stages of HBV replication ([Jones et al., 2013](#)). Tenofovir was originally synthesized in the mid 1980's and was initially shown to have anti-HIV activity. However, due to its very limited bioavailability the compound did not have the potential for widespread use. Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir that was developed to allow for oral administration of the drug. TDF was approved by the FDA for the treatment of HIV in 2001 and for the treatment of chronic HBV infection in 2008. The drug is marketed under the name Viread® by Gilead Sciences.



Gilead has developed tenofovir alafenamide fumarate (TAF) as a follow-on compound to TDF. TAF is reported to have greater antiviral activity than TDF along with better penetration into lymphoid tissues ([Eisenberg et al., 2001](#)). In addition, TAF exhibits similar efficacy to TDF but at much lower concentrations, as shown in a Phase 1 study where a TAF dose 10 times less than TDF offered superior antiviral activity ([Ruane et al., 2013](#)). Lastly, the higher intracellular concentration of tenofovir following metabolism of TAF supports the notion that kidney toxicity will be reduced compared to treatment with TDF. Gilead is currently testing TAF in two clinical trials for chronic HBV.

...CMX157...

CMX157 is a prodrug of tenofovir that utilizes a proprietary lipid technology developed by Chimerix, Inc. The proprietary technology is utilized to covalently modify a drug molecule with a lipid side-chain that mimics a naturally occurring phospholipid component of cell membranes. The lipid-conjugated molecule can then utilize natural uptake pathways to achieve oral bioavailability, enhance uptake into cells, avoid many toxicities, and yield higher intracellular concentrations of drug.



Source: ContraVir Pharmaceuticals, Inc.

Chimerix tested CMX157 in a Phase 1 trial in 2010. It was a randomized, double blind, placebo controlled, single dose escalation study conducted in healthy volunteers. The purpose of the study was to evaluate the safety, tolerability, and pharmacokinetics of CMX157. Along with CMX157, subjects were also dosed with Viread® to permit comparison of active tenofovir inside patient cells.

Data from the Phase 1 study showed that CMX157 was both safe and well tolerated. The data generated from the study support the notion that CMX157 may have a better safety profile than Viread® as the novel structure of CMX157 resulted in a high intracellular concentration of the active antiviral agent tenofovir diphosphate and decreased levels of circulating tenofovir, which means there is decreased potential for renal side effects associated with Viread®.

ContraVir has licensed CMX157 from Chimerix in exchange for an upfront payment of 120,000 shares of ContraVir preferred stock, valued at \$1.2 million (time of the deal). ContraVir intends to develop CMX157 for the treatment of chronic HBV infection and HIV. The company is planning to meet with the FDA to discuss an appropriate clinical plan for CMX157 and to initiate a Phase 2 clinical trial testing the compound in HBV patients in the next 12-18 months. A recently issued composition of matter patent for CMX157 provides intellectual property protection to at least 2031.

Financial Position and Capital Structure

At the end of the second quarter of FY 2015 (December 31, 2015) ContraVir reported \$8.8 million of cash. The company's cash position was strengthened by a recent private placement of 980,000 shares of Series A Convertible Preferred Stock that provided gross proceeds of \$9.8 million. The company's cash burn for the first and second quarters of FY 2015 was \$1.1 and \$1.4 million, respectively. We estimate the burn rate will increase in the coming quarters due to the initiation of the Phase 3 trial for FV-100. While we believe the company's current cash position will be enough to fund operations through the end of the calendar year 2015, we would not be surprised to see an additional financing in mid to late 2015.

The Series A Preferred Stock is convertible at any time into shares of common stock at a conversion price of \$0.48 per share, which represents 20.4 million shares. In addition, the company licensed CMX157 from Chimerix in exchange for 120,000 shares of Series B Preferred Stock, which are convertible into shares of common stock at a conversion price of \$1.12 per share, which represents 1.1 million shares.

The company reported 22.3 million shares outstanding as of February 9, 2015, and when adding in the 4.7 million warrants, 0.3 million currently exercisable stock options, and the shares upon conversion of the Series A and B Preferred Shares gives a fully diluted share count of 48.8 million. This gives the company a current fully diluted market cap of approximately \$200 million.

MANAGEMENT PROFILES

James Sapirstein, R.Ph., M.B.A. – Chief Executive Officer

Mr. Sapirstein has over 30 years of pharmaceutical industry experience. After beginning his career in 1984 as a sales representative with Eli Lilly, he accepted a position at Hoffmann-LaRoche in 1987, where he served for almost a decade as part of the sales and marketing teams. He held a number of positions at Hoffmann-LaRoche, including Product Director and International Operations Manager, and was actively involved with numerous product launches including several antivirals. In 1996, he became the Director of International Marketing of the Infectious Disease Division at Bristol Myers Squibb (BMS). Mr. Sapirstein directed the international HIV product marketing strategy at BMS and was an integral part of the international development and launch of a number of infectious disease products while at BMS.

More recently, Mr. Sapirstein has become known in the industry as a start-up and turnaround specialist, mainly for his work at Gilead Sciences, Inc. (GILD), Serono Laboratories, Inc., Tobira Therapeutics, Inc. and Alliqua Inc. (ALQA). Mr. Sapirstein served in the Global Marketing group at Gilead, beginning in 2000 where he led and developed the global marketing strategy for its flagship HIV drug, Viread. He played a key role in the development of the drug combination strategy that resulted in Gilead's acquisition of Triangle's nucleoside portfolio. That acquisition ultimately led to the launch of Truvada, Gilead's multi-billion dollar combination HIV drug. In 2002, he accepted the position of Executive Vice President for Serono Laboratories where he led a team of over 100 professionals to rebuild a struggling HIV and pediatric growth hormone business. As CEO of privately held Tobira Therapeutics, a New Jersey based biopharmaceutical company focused on the development of novel HIV and infectious disease compounds, he was instrumental in helping to raise over \$60 million in venture capital and research funding to enable Tobira to further its scientific development. As a result of those efforts, he was named one of New Jersey's top 50 most influential people in healthcare in 2010 by NJBiz.com. Most recently, Mr. Sapirstein was CEO of Alliqua Therapeutics at Alliqua Inc., where he helped lead the transformation of transdermal wound care and drug delivery technology into a premier wound care organization.

William Hornung – Chief Financial Officer

Mr. Hornung brings over 22 years of biopharmaceutical industry finance and operations leadership experience to ContraVir. Previously, Mr. Hornung held senior leadership positions at PTC Therapeutics Inc., most recently serving as Vice President of Finance. During his tenure at PTC Therapeutics (December 2002 through March 2014), Mr. Hornung oversaw the IPO process, in which PTC became a publicly traded company. Mr. Hornung also held positions of increasing responsibility with Elan Pharmaceuticals (formerly The Liposome Company) from 1998 through 2002. At Liposome and Elan, Mr. Hornung was responsible for strategic planning and operations of the company's UK-based European headquarters. Earlier in his career, Mr. Hornung worked for a clinical research organization where he was responsible for project management and all financial aspects of the company. Mr. Hornung holds a Bachelor of Science in Accounting from the William Paterson State University of New Jersey.

John Sullivan-Bolyai, MD – Chief Medical Officer

Dr. Sullivan-Bolyai brings many years of pharmaceutical and biotech experience as an expert in HBV. Prior to ContraVir, Dr. Sullivan-Bolyai was the Executive Director of Infectious Disease clinical research at Merck where he oversaw multiple HCV protocols in all three phases of clinical development. Prior to this, he was the Vice-President of Clinical Research at Idenix where he managed all medical aspects of the HIV and HCV programs. Additionally, he was responsible for the transition of Idenix's clinical team to Merck, which acquired Idenix. Prior to joining Idenix, Dr. Sullivan-Bolyai worked at Anadys Pharmaceuticals on hepatitis C and at Valeant Pharmaceuticals International on Valeant's nucleotide prodrug for the treatment of chronic Hepatitis B infection. Previously, he held various medical and operations positions at Biomeasure and Serono Laboratories in Massachusetts, working on coagulation, immunomodulatory, endocrine, and gastrointestinal compounds. He began his career with Hoffmann-La Roche where he worked on a variety of compounds for the treatment of bacterial infections, HCV and HIV. Dr. Sullivan-Bolyai received an MD, MPH from the University of Washington in Seattle. He completed his infectious diseases fellowship training at the Children's Orthopedic Hospital and Medical Center, Seattle, WA, followed by academic positions at UCLA and the University of Illinois.

VALUATION AND RECOMMENDATION

We are initiating coverage of ContraVir Pharmaceuticals, Inc. (NASDAQ: CTRV) with an Outperform rating and a price target of \$6.00. ContraVir is developing FV-100 for the treatment of herpes zoster (shingles) and the prevention of post-herpetic neuralgia (PHN). In addition, the company has in-licensed CMX157, a prodrug of tenofovir, a nucleotide analog inhibitor of viral reverse transcriptase that is currently approved for the treatment of human immune deficiency virus (HIV) and chronic hepatitis B virus (HBV) infection.

...Large Opportunity for FV-100...

The current treatment options for shingles include famciclovir, acyclovir, and valacyclovir. All of these compounds work similarly in that they inhibit replication of viral DNA by: 1) inhibiting viral DNA polymerase; 2) incorporating into and terminating the elongating DNA strand; and 3) inactivating the viral DNA polymerase. However, none of those compounds is currently approved for the treatment of shingles associated pain or PHN. While FV-100 appears to have a similar mechanism of action, ContraVir is hoping to position the compound as the first shingles medication that is approved for the prevention of PHN.

There are approximately one million shingles cases in the U.S. every year, with the incidence continuing to rise. This phenomenon could be due to an aging population or the increased use of the varicella vaccination, which may limit the re-exposure of individuals to VZV that can boost VZV-specific immunity. Regardless of the cause, a compound that could limit the incidence, severity, and/or duration of PHN would have the ability to gain a large market share in the treatment of shingles.

...The Phase 3 Results will be Key...

How successful FV-100 becomes will be entirely dependent upon the data from the Phase 3 trial and whether the compound is clearly differentiated from the currently available treatment options. In order to justify premium pricing compared to the generic medications now available, we believe that FV-100 will need to show clear efficacy in its ability to alter multiple aspects of PHN. Specifically, we believe there are three important parameters surrounding PHN that must be addressed, which are (in order of importance):

- ↳ The incidence of PHN
 - ↳ The severity of PHN
 - ↳ The duration of PHN

If FV-100 were shown to clearly and significantly modify PHN in those three areas, then ContraVir would have a highly successful drug. As we look ahead to the Phase 3 trial, we can imagine a number of scenarios that may occur based on the results:

- ✓ FV-100 demonstrates a statistically significant decrease in PHN incidence as well as a decrease in both the severity and duration of PHN in those who suffer from it. This is the best-case scenario for the company and would likely lead to favorable pricing and market penetration. Under this scenario we believe FV-100 has strong differentiating characteristics with peak potential sales in the \$700 million range.
- ✓ FV-100 demonstrates a statistically significant decrease in PHN incidence but does not affect the severity and duration of PHN. This is the most likely scenario and would still represent a sizable opportunity for ContraVir as we believe patients and physicians would still be quite open to a compound that decreased the chance of developing a debilitating condition such as PHN; however, we do not see as strong a pricing and reimbursement opportunity with FV-100. Under this scenario we believe FV-100 has peak potential sales in the \$450 million range.
- ✓ FV-100 does not cause a statistically significant decrease in PHN incidence, severity, or duration. This is the least likely scenario, as we believe based on the Phase 2 results that FV-100 has a good chance of at least decreasing the incidence of PHN. While this would represent the smallest opportunity for FV-100, the drug would likely still be utilized by a certain subset of physicians and patients. The last scenario would likely restrict any type of premium pricing or sizable market share for FV-100, and under this scenario we forecast peak sales of approximately \$250 million.

...Additional Upside Possible with CMX157...

Tenofovir is an inhibitor of reverse transcriptase, an enzyme involved in a number of diverse roles during different stages of HBV replication. However, due to its very limited bioavailability, the compound did not have the potential for widespread use. Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir that was developed to allow for oral administration of the drug. TDF was approved by the FDA for the treatment of HIV in 2001 and for the treatment of chronic HBV infection in 2008. The drug is marketed under the name Viread® by Gilead Sciences. We estimate that approximately \$500 million in sales of Viread® are for the treatment of HBV infections.

CMX157 is a prodrug of tenofovir that utilizes a proprietary lipid technology developed by Chimerix, Inc. The proprietary technology is utilized to covalently modify a drug molecule with a lipid side-chain that mimics a naturally occurring phospholipid component of cell membranes. The lipid-conjugated molecule can then utilize natural uptake pathways to achieve oral bioavailability, enhance uptake into cells, avoid many toxicities, and yield higher intracellular concentrations of drug. Data from Phase 1 studies suggests CMX157 may have lower toxicity than Viread® and the potential for reduced renal side effects.

Superior efficacy and a more benign safety profile would likely mean that CMX157 could take a significant market share from Viread® for the treatment of HBV infections. However, Gilead has developed tenofovir alafenamide fumarate (TAF) as a follow-on compound to TDF. TAF is reported to have greater antiviral activity than TDF along with better penetration into lymphoid tissues. In addition, TAF exhibits similar efficacy to TDF but at much lower concentrations, as shown in a Phase 1 study where a TAF dose 10 times less than TDF offered superior antiviral activity. Lastly, the higher intracellular concentration of tenofovir following metabolism of TAF supports the notion that kidney toxicity will be reduced compared to treatment with TDF.

Even if CMX157 has superior efficacy and reduced side effects compared to Viread®, in order to gain appreciable market share it will be necessary for CMX157 to also exhibit characteristics at least on par with TAF, if not better. At this juncture we are assuming that CMX157 will have equivalent efficacy to TAF, which will enable the compound to capture some portion of the market.

Potential upside for CMX157 exists with the possibility of combination therapies, particularly since the patent life for CMX157 extends to 2031, thus giving ContraVir an extended amount of time to test out various combination therapies. While a potential positive for the value of CMX157, at this juncture it is not possible to include potential combination therapies in our valuation model.

Valuation methodology

For FV-100 we model that the -007 trial will conclude in 2016, with an NDA filing in 2017, and approval by the FDA in 2018. We have performed a weighted average discounted cash flow analysis that takes into account the three scenarios discussed above, the likelihood for each outcome, and the pricing/peak market share for each outcome:

- Best = 25% probability, 32% peak market share, \$350 / Rx
- Base = 50% probability, 25% peak market share, \$290 / Rx
- Lowest = 15% probability, 19% peak market share, \$210 / Rx
- Failure = 10% probability, not approved

We use a 22% discount rate and model sales out to 2028, when the FV-100 composition of matter patent expires. Estimated peak revenues under each of the scenarios are: Best = \$700 million; Base = \$450 million; Lowest = \$250 million. This leads to a current valuation for FV-100 of \$285 million.

For CMX157, we estimate that a Phase 2 trial gets underway in 2015, a Phase 3 trial in 2017, with an NDA filing and approval in 2019 and 2020. For modeling, we estimate that CMX157 will be as efficacious as TAF, thus we forecast that the drug would cost \$12,000 per year in 2015 (the approximate current cost of Viread®), with inflationary increases for the ensuing years. We model peak market share of 20%, which we believe would occur in 2023 and would generate approximately \$200 million in revenue. We apply a 22% discount rate and assign a 33% probability of approval. This leads to a current valuation for CMX157 of \$31 million.

We combine the valuations for FV-100 and CMX157 along with the company's current cash position of \$8.8 million and an estimated \$25 million of capital requirements to arrive at a present value for ContraVir of \$300 million. The company currently has a fully diluted share count of 48.8 million (See "Financial Position and Capital Structure"), which leads to a fair value of approximately \$6.00 per share.

Potential Risks to our Thesis

FV-100 is not superior to valacyclovir in any outcome in the 007 trial: While we do not believe that this is a likely outcome, based upon the clear trends toward superiority in the Phase 2 trial, there is still a possibility that FV-100 will not show superiority to valacyclovir in any of the outcomes regarding PHN. If this were to occur, we would be forced to drastically reduce our valuation of ContraVir, as the majority of the company's value at this point is in FV-100.

CMX157 does not show efficacy in treating chronic HBV infections, or is not differentiated from TAF: CMX157 has only been tested in a Phase 1 trial in healthy volunteers, thus we do not have any data on how patients with chronic HBV infections will respond to treatment. In addition, with TAF currently in Phase 3 trials for treating chronic HBV infections, that compound could have a "first to market" advantage. In order to gain appreciable market share, CMX157 will need to be at least as effective as TAF in regards to treatment and decreased side effects.

PROJECTED FINANCIALS

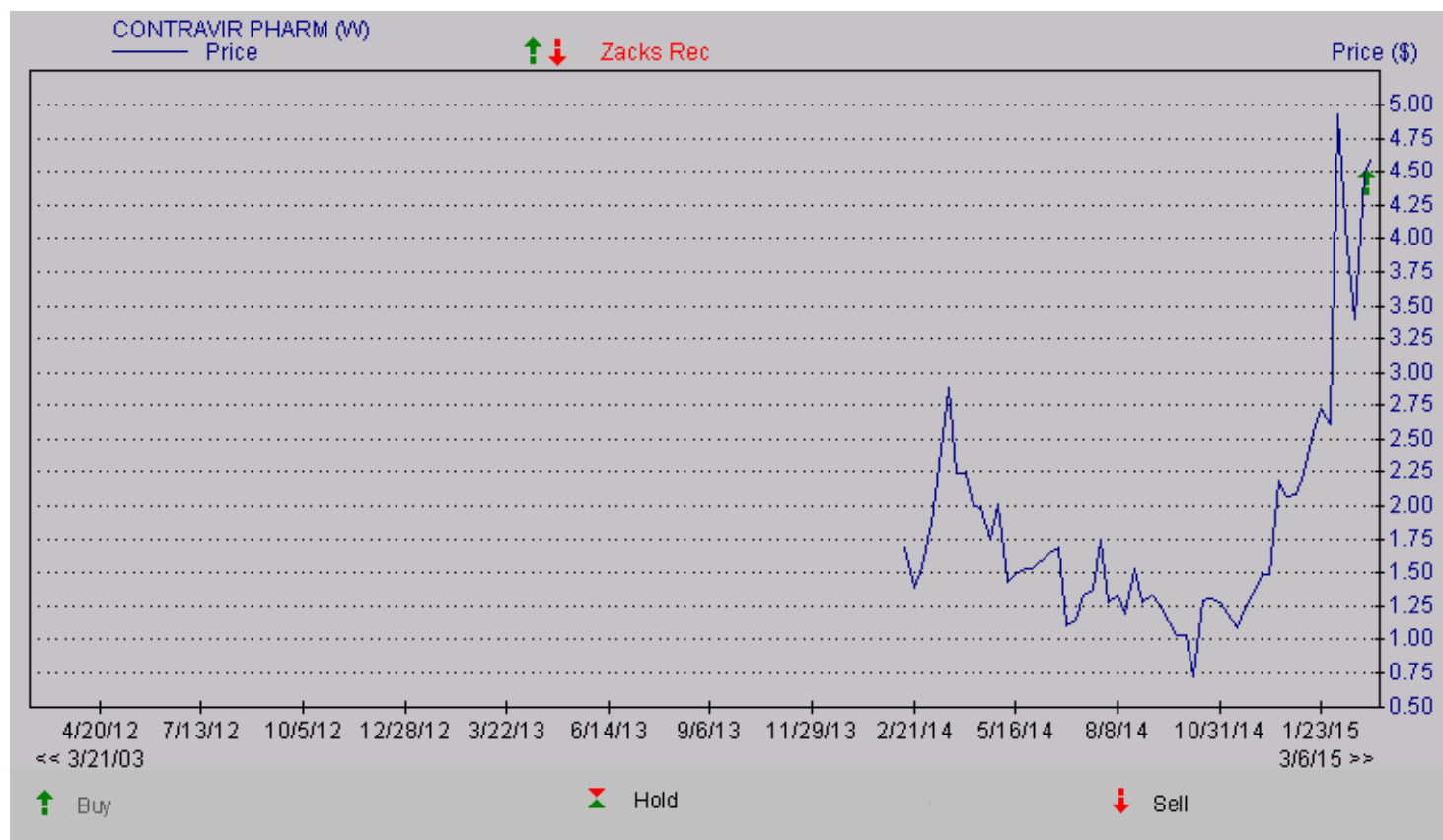
ContraVir Pharmaceuticals, Inc. Income Statement

ContraVir Pharmaceuticals, Inc.	FY'14A	Q1A	Q2A	Q3E	Q4E	FY'15E	FY'16E	FY'17E
FV-100	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
<i>YOY Growth</i>	-	-	-	-	-	-	-	-
CMX-157	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
<i>YOY Growth</i>	-	-	-	-	-	-	-	-
Collaborations / Licensing	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
<i>YOY Growth</i>	-	-	-	-	-	-	-	-
Total Revenues	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
<i>YOY Growth</i>	-	-	-	-	-	-	-	-
CoGS	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
<i>Gross Margin</i>	-	-	-	-	-	-	-	-
General & Administrative	\$1.4	\$0.7	\$1.3	\$1.4	\$1.4	\$4.8	\$6.0	\$7.5
Rsearch & Development	\$0.3	\$0.4	\$1.8	\$1.8	\$1.9	\$5.9	\$8.0	\$10.0
Other expenses	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Operating Income	(\$1.7)	(\$1.1)	(\$3.1)	(\$3.2)	(\$3.3)	(\$10.7)	(\$14.0)	(\$17.5)
<i>Operating Margin</i>	-	-	-	-	-	-	-	-
Changes in Derivative Liability	(\$3.6)	(\$0.4)	\$0.0	(\$0.1)	(\$0.1)	(\$0.6)	(\$2.0)	(\$2.0)
Interest Income (Expense)	(\$0.0)	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Pre-Tax Income	(\$5.3)	(\$1.5)	(\$3.1)	(\$3.3)	(\$3.4)	(\$11.3)	(\$16.0)	(\$19.5)
Preferred Stock Conversion Feature	\$0.0	\$0.0	(\$4.8)	(\$0.3)	\$0.0	(\$5.1)		
Taxes & Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
<i>Tax Rate</i>	0%	0%	0%	0%	0%	0%	0%	0%
Net Income	(\$5.3)	(\$1.5)	(\$7.9)	(\$3.6)	(\$3.4)	(\$16.4)	(\$16.0)	(\$19.5)
Reported EPS	(\$0.41)	(\$0.07)	(\$0.36)	(\$0.14)	(\$0.12)	(\$0.68)	(\$0.53)	(\$0.49)
<i>YOY Growth</i>	-	-	-	-	-	-	-	-
Wte Ave Shares Outstanding	12.8	20.2	22.3	26.0	28.0	24.1	30.0	40.0

Source: Zacks Investment Research, Inc.

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