Zacks Small-Cap Research

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Nuvo Research, Inc. (T.NRI - TSX)

T.NRI: Initiating coverage of Nuvo Research, Inc., Low Risk With Big Upside.

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	05/05/2014
Current Price (05/05/14)	$3.26
Target Price	**$7.50**

INITIATION

We are initiating coverage of Nuvo Research, Inc. (TSX: NRI) with a Buy rating and a $7.50 price target.

Nuvo is a Canadian specialty pharmaceutical company with a diverse portfolio of marketed products including Pennsaid and Pennsaid 2% for treatment of knee osteoarthritis, as well as Synera and Pliaglis for local dermal analgesia prior to superficial dermatological procedures. The company also has a set of technologies to increase skin permeability of drug compounds. Lastly, Nuvo is developing an immunomodulatory compound, WF10, for treatment of allergic rhinitis with the possibility to tap into a potential $10 billion market.

With $14 million in cash and $18 million in 2013 revenues, Nuvo has tremendous upside potential.

SUMMARY DATA

52-Week High	**4.70**
52-Week Low	**1.30**
One-Year Return (%)	**0.31**
Beta	**1.14**
Average Daily Volume (sh)	**19.1**
Shares Outstanding (mil)	**8.9**
Market Capitalization ($mil)	**28.8**
Short Interest Ratio (days)	**1.1**
Institutional Ownership (%)	**N/A**
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 2013 Estimate	**N/A**
P/E using 2014 Estimate	**N/A**

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

ZACKS ESTIMATES

Revenue

(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	$2.3 A	$3.3 A	$9.1 A	$3.7 A	$18.4 A
2014	$2.8 A	$3.3 E	$3.4 E	$3.4 E	$12.9 E
2015					$14.0 E
2016					$18.0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	-$0.39 A	-$0.25 A	-$0.34 A	-$0.22 A	-$1.18 A
2014	-$0.31 A	-$0.25 E	-$0.29 E	-$0.32 E	-$1.15 E
2015					-$1.01 E
2016					-$0.69 E

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WHAT'S NEW

Initiating Coverage



We are initiating coverage of Nuvo Research, Inc. (TSX: NRI; OTC: NRIFF) with a Buy rating and a $7.50 price target.

Nuvo is a specialty pharmaceutical company with a diverse portfolio of products and technologies. The company has two separate business units: Topical Products and Technology (TPT) Group and the Immunology Group. The TPT Group has four marketed products and a pipeline of products at various stages of development. The primary focus of this group is pain and dermatology. In addition, TPT has four topical and transdermal drug delivery platforms. The Immunology Group has two commercialized products, a developmental program for the treatment of allergic rhinitis, and a potential immune modulating platform.

TPT commercial products include four FDA-approved drugs, Pennsaid, Pennsaid 2%, HLT Patch, and Pliaglis.

- *Pennsaid*®: A treatment for the signs and symptoms of knee osteoarthritis (OA) that combines a transdermal carrier (dimethyl sulfoxide, DMSO) with diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID) and delivers the drug through the skin directly to the site of pain and inflammation.
- *Pennsaid® 2%*: A follow-on product to Pennsaid® that contains 2% diclofenac sodium compared to 1.5% for original Pennsaid. Pennsaid 2% is a more viscous product, supplied in a metered dose pump bottle, and has been approved for twice daily dosing compared to four times a day for regular Pennsaid®. In addition, Nuvo has extended patent protection on Pennsaid® 2% with 5 orange book listed patents with expiry dates ranging from 2027 to 2030.
- *HLT Patch*: A topical patch the combines lidocaine, tetracaine, and heat using the company's proprietary Controlled Heat-Assisted Drug Delivery (CHADD™) technology. The CHADD™ unit generates heat and contributes to the efficacy of HLT Patch (sold as Synera® by U.S. licensee Galen and Rapydan® by Eurocept). The patch is applied to the skin approximately 20 to 30 minutes prior to a painful medical procedure, such as blood draws, needle injections, and minor dermatological procedures.
- *Pliaglis*®: A self-occluding topical local anesthetic cream that provides local dermal analgesia on intact skin prior to superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, and laser-assisted tattoo removal. It consists of a proprietary formulation of lidocaine and tetracaine, and utilizes Nuvo's phase-changing topical cream Peel technology, which when applied to a patient's skin dries to form a pliable layer that releases drug into the skin.

The company's Immunology group is focused on the development of WF10, a composition for the treatment of immune related disorders.

- *WF10*: WF10 is a solution of OXO-K993 that appears to act on macrophages and how they regulate the immune system. WF10 may rebalance improperly functioning immune systems and is currently being investigated as a treatment for allergic rhinitis, a potential $10 billion market.
- *Oxoferin*®: Oxoferin® is a topical wound healing agent that is a diluted form of WF10. Research to date suggests that Oxoferin® has a positive impact on wound healing and leads to contraction, closure and faster healing of wounds. Oxoferin® is currently marketed by Nuvo Manufacturing GmbH in the E.U., and its partners in Asia and South America.

Our model indicates that Nuvo is currently worth approximately $7.50 per share without factoring in potential revenues from the approval of WF10 for the treatment of allergic rhinitis. What this means is at the current price of $7.50, an investor is getting a company with a solid portfolio of revenue producing products with an experimental compound to treat allergies for free.

INVESTMENT THESIS

PENNSAID® and PENNSAID® 2%

…Knee Osteoarthritis…

Osteoarthritis (OA) is the most common form of arthritis that affects approximately 250 million adults worldwide (Vos et al., 2006). It results in a slow degeneration of the joint through a gradual wearing away of the joint cartilage. It mostly affects weight-bearing joints (i.e., the hips, knees, and ankles) and results in their progressive deterioration. OA affects articular cartilage, which is the smooth, white tissue that covers the ends of bones where they come together to form a joint. Articular cartilage is characterized by a very low friction and a high resistance to wear; however, it also has poor regenerative properties. In addition to articular cartilage, the knee joint contains a second type of cartilage called menisci that act as shock absorber pads while joint fluid adds lubrication to the joint.

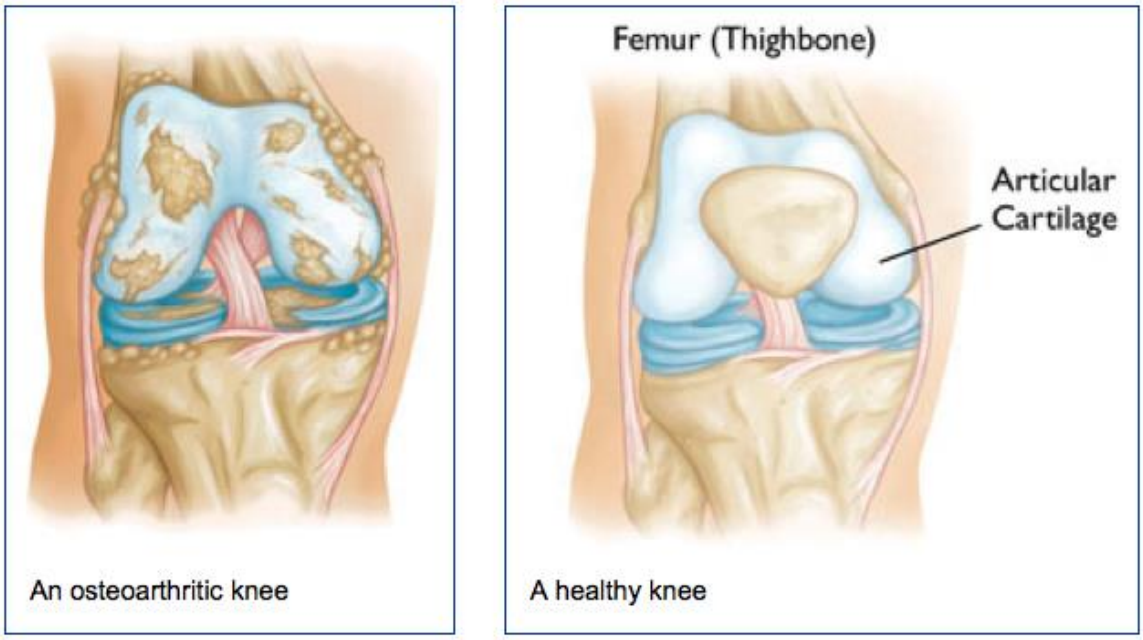


Figure 1: An osteoarthritic knee compared to a healthy knee. *Source*: AAOS

In patients suffering from OA, there is a cartilage failure that leads to a limited range of motion, bone damage, and severe pain. Knee OA starts as the lack or loss of articular cartilage and progresses to involvement of the surrounding bone, tissues, and joint fluid. It results in progressive loss of function including: gait, stair climbing and other physical activities that involve the lower limbs such as walking.

There are approximately 27 million people in the United States who suffer from OA, with the knee being one of the most common areas affected in older individuals. While it has been known to occur in young people, it typically affects those aged 45 and over and is considered as one of the leading causes of lower limb disabilities among the elderly. In addition, as a result of the major loss of function and, due to how it limits activity, OA can also result in depression and a loss of independence. There is also a considerable socioeconomic burden on societies and families due to disabilities brought about by OA.

People with knee OA experience loss of proprioception, which may affect postural stability and risk of fall. Postural stability is defined as the control over the body's position in space for orientation and balance purpose. Postural stability (static and dynamic balance) is essential during activities of daily living and ambulation. Impaired postural stability is one of the main reasons of falls in older adults and constitutes a significant public health problem; and, it is considered as one of the leading causes of hospital admissions.

As there is no cure for OA, treatment is focused on controlling symptoms and preserving physical function. This is accomplished through a combination of pharmacological and non-pharmacological therapies and ultimately joint replacement therapy.

Even with effective management strategies available, OA is both under-diagnosed and under-treated. This may be due in part to the high co-morbidities associated with OA, with upwards of 90% of OA patients suffering from at least one other chronic condition. OA and cardiovascular disease (CVD) are among the most common dyads seen in clinical practice, with CVD precluding the use of OA therapies – particularly non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, ketoprofen, or diclofenac.

If left untreated, most patients manage the pain associated with OA by limiting physical activities that exacerbate the pain, such as walking. This limitation of physical activity can then lead to poorer overall health, a higher risk of CVD and worsening of other chronic conditions.

…Current Treatment Options for Knee OA…

Treatment options for Knee OA can be divided into two groups: Nonsurgical and Surgical. Nonsurgical treatment options include:

- **Exercise and weight loss**: Weight loss is the first recommendation for patients suffering from knee OA, as each extra pound of weight can add 6 pounds of pressure on the knee joint during activity. Muscle strength is another effective means of controlling OA, as the muscles surrounding the knee act as shock absorbers and the stronger the muscles then the more stress they can absorb for the knee.
- **Braces**: Knee braces are available for OA that specifically affects the medial (inside) portion of the knee joint. The braces are custom made and can be quite expensive.
- **Nutritional supplements**: Glucosamine sulfate and chondroitin sulfate are widely used; however, neither of these treatments is regulated by the FDA and we could not find any randomized controlled trials demonstrating superiority of their use over placebo.
- **Viscosupplementation**: This involved the use of Hyaluronic acid injected directly into the cavity around the knee joint. Currently, there are five FDA approved HA injections currently available. Clinical results have been mixed, with only ~50% of patients experiencing symptomatic relief.
- **Cortisone injections**: Injection of cortisone directly into the knee has been shown to be effective for "flares" of arthritis symptoms. However, repeated cortisone injections are known to cause articular cartilage deterioration thus the injections are used sparingly in the knee joint.
- **Medications**: Anti-inflammatory medications are known to decrease symptoms associated with knee OA. NSAIDs, including aspirin, ibuprofen and naproxen, are known to be the most effective of the oral medications with stomach irritation being the most common side effect. Less common side effects of NSAIDs include stomach ulceration and renal damage.

Surgical treatment options include:

- **Chondroplasty**: An arthroscopic procedure performed to repair a small area of damage through smoothing of the articulate cartilage. This is only utilized in cases where there is mild-to-moderate cartilage wear.
- **Abrasion/Microfracture**: This procedure is for small areas where there is exposed bone or complete loss of cartilage. The exposed bone is abraded, causing it to bleed and stimulating the growth of fibrocartilage. It has been used successfully in patients who will be receiving a total knee replacement, and can put off the necessity of a total knee replacement for up to 5 years.
- **OATS procedure**: Osteochondral autograft (or allograft) transplant (OATS) can be performed for both small and large area of full thickness surface cartilage loss. The procedure involves removing a piece of bone that lacks surface cartilage and replacing it with a similar sized piece of bone with intact articular cartilage.
- **Osteotomy**: Patients with knee OA often have arthritis in either the inside or outside portion of the knee, causing a mis-alignment of the knee joint. An osteotomy is performed by wedging open either the tibia or femur and adding bone graft puddy to stimulate new bone growth in the wedged area. The procedure is typically very successful in relieving symptoms and preventing or delaying total knee replacement.
- **Knee replacement**: For severe OA, total knee replacement involves capping the end of the femur and tibia with metal components that recreate the surface of the joint. A plastic spacer is then inserted between the metal pieces to create a smooth gliding surface. Greater than 90% of patients experience a significant or total loss of knee pain. The procedure can cost upwards of $50,000 in the U.S.

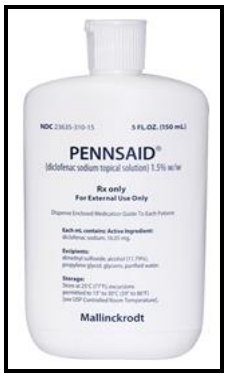
The American Academy of Orthopaedic Surgeons (AAOS) published newly revised guidelines for knee OA in 2013. The most significant change from the previous guidelines issued in 2008 was a strong recommendation against the use of hyaluronic acid viscosupplementation. The reason for this was that a meta-analysis of 14 studies assessing HA injections did not have enough evidence to meet the minimum clinically important improvement thresholds. Another important point from the newly published guidelines was a strong recommendation for the use of NSAIDs.

…Pennsaid® is a topical NSAID treatment for knee OA…

NSAIDs are often used for the treatment of OA, particularly for knee OA. They block cyclooxygenase-1 and -2 (COX-1, COX-2) enzymes, thereby inhibiting the production of prostaglandins, which are known inducers of pain and inflammation. When administered orally, NSAIDs are effective in reducing pain and decreasing inflammation; however, they have well documented side effects related to systemic administration.

The dose-related gastrointestinal side effects are a result of the inhibition of the COX-1 enzyme, which is responsible for the normal gastro-protective processes (Roth, 1988). Dyspepsia, abdominal pain, and nausea are all common side effects of oral NSAIDs (Makris *et al*. 2010). While these adverse events are manageable, more serious events are known to occur with oral NSAID use including upper gastrointestinal bleeding, ulcers, and death (Hernández-Díaz *et al*., 2000). Both nonselective and COX-2 selective NSAIDs (e.g., celecoxib and rofecoxib) are known to increase the risk of myocardial infarction, stroke and death (Antman et al. 2007). Thus, the rational for a topical formulation of a NSAID is that the drug can be administered locally while minimizing systemic side effects.

Nuvo has developed Pennsaid® for the treatment of the signs and symptoms associated with knee OA. Pennsaid® is a topical formulation that combines the transdermal carrier dimethyl sulfoxide (DMSO) with diclofenac sodium, a NSAID, which delivers the drug through the skin directly to the sight of inflammation and pain. Pennsaid® first gained FDA approval in November 2009 and was commercially launched by the company's partner Mallinckrodt, Inc. (then a subsidiary of Covidien) in April 2010. Pennsaid® is also available for sale in Canada, Greece, Italy and the United Kingdom.



Pennsaid® was tested in greater than 6,000 patients that included seven separate Phase 3 studies. The two adequate and well-controlled studies that the U.S. FDA based its approval decision in part on were PEN-03-112 and RA-CP-109-US. We discuss these studies and their data below.

…PEN-03-112…

Study PEN-03-112 was a Phase 3, 84 day (12 week), oral and topical placebo and topical vehicle controlled, double-blind, parallel design, multi-center, randomized trial conducted in 40 centers in Canada and 21 centers in the U.S. The study was designed to evaluate the efficacy and safety of Pennsaid® in patients with knee OA. The trial consisted of 775 patients randomized into five groups:

1. Pennsaid® + oral diclofenac ("combination" arm) – 152 patients
2. Pennsaid® + oral placebo ("Pennsaid" arm) – 154 patients
3. Vehicle-control solution (45.5% DMSO) + oral placebo ("vehicle control" arm) – 161 patients
4. Placebo solution (2.3% DMSO) + oral placebo ("placebo" arm) – 157 patients
5. Placebo solution + oral diclofenac ("oral diclofenac" arm) – 151 patients

Pennsaid® was administered at 40 drops four times daily applied to the skin surrounding the knee joint. The topical placebo formulation contained 2.3% DMSO to preserve study blinding (historically, DMSO has been documented to cause halitosis/taste perversion in a small number of patients) and was administered at the same dose and regimen (40 drops four times daily). Oral treatment contained either 100 mg diclofenac once daily or oral placebo. The patients in the vehicle control arm received a topical formulation similar to Pennsaid® except it lacked the active ingredient, diclofenac sodium. Only one knee was treated per patient regardless of the symptoms of the other knee. The randomization was stratified according to whether patients had one or both knees affected by OA.

The study had three co-primary endpoints: changes in WOMAC (Western Ontario and McMaster Universities Arthritis Index) dimension of pain, physical function, and change in Patient Overall Health Assessment Question (POHA) at the 12 week final study visit. WOMAC is a widely used and standardized set of questionnaires used by doctors to evaluate the condition of patients with OA of the knee and hip. The analysis includes pain, stiffness, and physical functioning of joints. The WOMAC measures five items for pain, two for stiffness, and 17 for physical function. Each question for the pain dimension scale is given a weight of 4 points (0-none, 1-mild, 2-moderate, 3-severe, 4-extreme) resulting in a 20-point scale. The physical function scale questions are also given a weight of 4 points for a 68-point scale. The POHA question asked "*Considering all the ways your osteoarthritic (study) knee and its treatments affect you, including both positive and negative effects, how would you rate your overall state of health in the past 48 hours?*" with possible answers on a scale of 0-4 (0-very good, 1-good, 2-fair, 3-poor, 4-very poor). A clinically important secondary outcome was set as a 10% absolute change on each scale.

The primary outcome of the study was comparison of changes from baseline to final study assessment at 12 weeks in the three co-primary endpoints between the "Pennsaid" group and the "placebo" group. Table 1 shows the efficacy results for the primary endpoint for all five study arms. Patients treated with Pennsaid® had greater relief of pain than patients treated with placebo on the 20-point scale (6.0 vs. 4.7, *P* = 0.015). Each of the groups had a considerable change from baseline at the 12-week assessment, and the 1.3 difference between Pennsaid® treated and placebo groups was modest but still statistically significant. There was also a statistically significant benefit compared to placebo-treated patients for the other co-primary endpoints, physical function and POHA.

Table 1: Efficacy analysis for Study PEN-03-112

Variable	Group 1 PEN+OD N=151	Group 2 PEN+OP N=154	Group 3 VC+OP N=161	Group 4 P+OP N=155	Group 5 P+OD N=151	*P*-value 2 vs 4	*P*-value 2 vs 3
WOMAC pain score Mean change (SD)	-6.95 (4.76)	-6.02 (4.54)	-4.70 (4.31)	-4.74 (4.35)	-6.43 (4.11)	0.0150	0.0094
WOMAC physical function Mean Change (SD)	-18.69 (14.03)	-15.75 (15.14)	-12.13 (14.58)	-12.34 (14.72)	-17.88 (14.33)	0.0344	0.0255
POHA Mean Change (SD)	-0.95 (1.21)	-0.95 (1.30)	-0.65 (1.12)	-0.37 (1.04)	-0.88 (1.31)	<0.0001	0.0158

PEN+OD = Pennsaid® plus oral diclofenac
PEN+OP = Pennsaid® plus oral placebo
VC+OP = vehicle control plus oral placebo
P+OP = topical placebo plus oral placebo
P+OD = topical placebo plus oral diclofenac

A comparison of group 2 (Pennsaid® plus oral placebo) to group 5 (topical placebo plus oral diclofenac) and group 1 (combination of Pennsaid® and oral diclofenac) allowed for a comparison between topical and oral diclofenac. In general, there was a numerically greater improvement in patients receiving oral diclofenac than those receiving Pennsaid; however, the difference was not statistically significant. The combination of oral diclofenac and Pennsaid® (group 1) resulted in somewhat improved efficacy compared to oral diclofenac alone, though the differences were also not statistically significant.

Data from intermediate time points were examined to determine the time course of clinical benefit seen with Pennsaid® treatment. Table 2 shows the mean changes from baseline to week 4, week 8 and week 12 in patients treated with Pennsaid®. The data showed that the effect of treatment was evident as early as week 4 and the effect at week 4 was higher that that of placebo at week 12 (5.26 at week 4 with Pennsaid vs. 4.74 at week 12 with placebo).

Table 2: Mean changes in endpoints observed at different time points in patients treated with Pennsaid

Variable	4 week minus baseline	8 week minus baseline	12 week minus baseline
WOMAC pain score Mean change (SD)	-5.26 (4.31)	-5.81 (4.42)	-6.02 (4.54)
WOMAC physical function Mean Change (SD)	-13.19 (13.06)	-14.75 (14.61)	-15.75 (15.14)
POHA Mean Change (SD)	-0.75 (1.19)	-0.79 (1.29)	-0.95 (1.30)

Most adverse events (AEs) were minor and there were very few reports of serious AEs. The most common adverse event (AE) reported in Pennsaid® treated patients compared to placebo was application site skin reaction (32% vs. 5% for dry skin and 9% vs. 2% for contact dermatitis). Gastrointestinal (GI) related events occurred at higher rates in the oral diclofenac group compared to the Pennsaid® group. This was expected and validates the hypothesis that use of topical NSIADs are safer than oral NSIADs due to less systemic exposure.

…RA-CP-109US…

Study RA-CP-109US was conducted at 43 centers in the U.S. with 362 patients randomized into two groups: Pennsaid® treated (n = 164) or DMSO Vehicle treated (n = 162). The 109-US study was conducted just as the PEN-03-112, with the same inclusion and exclusion criteria, the same amount of Pennsaid® administered and the same co-primary endpoints. Table 3 shows the efficacy results for the three co-primary endpoints. The observed effect sizes of both Pennsaid® and Vehicle control appear to be similar to the effect sizes seen in Study PEN-03-112. The effect due to Pennsaid® treatment was also modest (1.5 for pain dimension and 5 for physical function) but was statistically significantly higher than vehicle control.

Table 3: Efficacy analysis for Study RA-CP-109-US

Variable	Pennsaid N=164	Vehicle Control N=162	*P*-value
WOMAC pain score Mean change (SD)	-5.9 (4.7)	-4.4 (4.4)	0.0017
WOMAC physical function Mean Change (SD)	-15.3 (15.2)	-10.3 (13.9)	0.0024
POHA Mean Change (SD)	-1.3 (1.2)	-1.0 (1.1)	0.0052

…Pennsaid offers equivalent pain relief to oral diclofenac with fewer GI-related side effects…

In order to compare the efficacy of Pennsaid® to oral diclofenac, study RA-CP-110 conducted in Canada in 2001-2002 tested both compounds in a group of 622 men and women who were treated with either Pennsaid® 50 drops t.i.d. plus an oral placebo or a placebo topical solution and oral diclofenac (Tugwell *et al*., 2004). Results showed that the differences between the two treatments all fell within the predefined equivalence ranges, meaning that the reduction in pain produced by Pennsaid® was equivalent to oral diclofenac.

…Efficacy Conclusions…

The following conclusions can be drawn from about Pennsaid:

- ⇨ A statistically significant benefit was seen in the treatment of knee OA with Pennsaid® compared to placebo in the WOMAC pain and physical function dimensions and POHA.
- ⇨ The effect of Pennsaid® in treatment of knee OA was seen as early as 4 weeks and was maintained for up to 12 weeks of treatment.
- ⇨ Pennsaid offers equivalent efficacy to oral diclofenac with fewer GI-related side effects.

Based on the available clinical data, **WE CONCLUDE** that Pennsaid® is a valuable asset for Nuvo's portfolio as it is effective in treating mild to moderate knee OA, has relatively few side effects and has a better safety profile than oral diclofenac while providing equivalent pain relief.

…Enter Pennsaid® 2%…

Pennsaid® 2% is a follow-on product to original Pennsaid® and contains 2% diclofenac sodium compared to 1.5% for original Pennsaid®. Pennsaid® 2% is more viscous than original Pennsaid®, supplied in a metered dose pump bottle, and has been approved in the U.S. for twice daily dosing compared to four times a day for Pennsaid® and its chief competitor, Voltaren® Gel. Nuvo has new patents covering Pennsaid® 2% in the U.S. that extend the intellectual property protection to 2030. A patent was also issued in the E.U. that provides protection for Pennsaid® 2% formulation and its use.

Pennsaid® 2% was evaluated in a Phase 2 randomized, double-blind, vehicle-controlled, parallel-group clinical study to evaluate the safety and efficacy of the compound for the treatment of knee OA. Patients were treated at a dose of 2 pumps twice a day for four weeks. The primary endpoint was change in WOMAC pain intensity comparing Pennsaid® 2% treated patients with those treated with vehicle only. Table 4 shows the efficacy results from the study, with patients treated with Pennsaid® 2% experiencing a greater reduction in the WOMAC pain scale compared to patients treated with vehicle.

Table 4: Efficacy analysis for Pennsaid® 2% Phase 2 study

Variable	Pennsaid N=130	Vehicle Control N=129	*P*-value
WOMAC pain subscale			
Baseline	12.4	12.6	
Mean Change from Baseline	-4.5	-3.6	0.042

…Disagreements with Mallinckrodt over Pennsaid® 2% Development Pathway…

In June 2009, Nuvo entered into a U.S. Licensing Agreement with Mallinckrodt, granting Mallinckrodt exclusive rights to market and sell Pennsaid® in the U.S. through the transfer of the NDA to Mallinckrodt upon FDA approval in the U.S.

Under the terms of the agreement, Nuvo received a non-refundable, upfront payment of $11.3 million (U.S. $10.0 million) upon signing the U.S. Licensing Agreement. Upon FDA Approval in November 2009, the company received a $16.0 million (U.S. $15.0 million) milestone payment and shortly thereafter transferred ownership of the Pennsaid® NDA to Mallinckrodt. Under the terms of the U.S. Licensing Agreement, Mallinckrodt assumed responsibility for all development activities and costs related to Pennsaid® subsequent to the Effective Date and subsequent to the transfer of the NDA all regulatory responsibility. Nuvo is entitled to receive 20% royalties on net U.S. sales of Pennsaid®.

When Nuvo signed the U.S. Licensing Agreement with Mallinckrodt in June 2009 for Pennsaid®, they also negotiated and agreed to a development plan for Pennsaid® 2%. This plan called for specific development activities to be conducted by Mallinckrodt and timelines for carrying out these activities. The development plan included a Phase 2 clinical trial, the results of which are discussed above, which was to be followed immediately by two Phase 3 clinical trials. Under terms of the U.S. Licensing Agreement, Mallinckrodt assumed full responsibility for managing, planning, executing, and paying for all development activities for Pennsaid® 2%. Mallinckrodt provided the final results of the Phase 2 trial for Pennsaid® 2% to Nuvo in June 2011, with results showing that Pennsaid® 2% met its primary endpoint of reducing knee OA pain.

The Pennsaid® 2% development plan had provided that two Phase 3 pivotal clinical trials were to have commenced no later than February 2011, and that if this timeline was not met then Nuvo had the right to terminate the licensing agreement as it relates to Pennsaid® 2% and to take back U.S. rights to the product. In June 2011, Mallinckrodt advised Nuvo that it was pursuing a Supplementary New Drug Application (sNDA) regulatory approval pathway for Pennsaid® 2% using the data from the Phase 2 clinical trial rather than a New Drug Application (NDA) supported by two Phase 3 clinical trials, as was specified by the development plan. Mallinckrodt reasoned that the Phase 2 clinical data would be enough to support the sNDA and that the sNDA could be filed sooner than a new NDA. Mallinckrodt then requested that Nuvo formally alter the development plan to reflect this new strategy. Under the terms of the License Agreement any changes to the development plan required the unanimous consent of the Joint Steering Committee (JSC) that had half Nuvo and half Mallinckrodt representatives. Mallinckrodt presented their proposal to eliminate the two Phase 3 studies to the JSC and Nuvo formally refused to provide its consent.

Nuvo believed that the new regulatory pathway was riskier than the pathway agreed upon in the original development plan, and that the Phase 2 clinical trial was not designed or powered as a pivotal study to support approval. Nuvo management noted Mallinckrodt's new plan would deprive Nuvo of the benefit of Phase 3 clinical data to be used in support of regulatory filings outside the U.S. Under the terms of the License Agreement, Nuvo was explicitly entitled to use the Phase 3 data to gain approval for Pennsaid 2% outside of the U.S.

In May 2012, Mallinckrodt submitted a sNDA for Pennsaid® 2% to the FDA. In July 2012, the FDA requested that Mallinckrodt withdraw the sNDA and refile it as a full NDA. Mallinckrodt then resubmitted the application as a NDA in July 2012, which the FDA accepted for review with a Prescription Drug User Fee Act (PDUFA) date of March 4, 2013. Mallinckrodt received a Complete Response Letter (CRL) to the NDA for Pennsaid® 2% in which the FDA confirmed that the only requirement was the completion of a pharmacokinetic (PK) study comparing Pennsaid® 2% to original Pennsaid®. Mallinckrodt completed the additional PK study and in August 2013 submitted the study to the FDA to address the CRL. On January 16, 2014, the FDA approved the sale and marketing of Pennsaid® 2% in the U.S. along with a 3-year marketing exclusivity for Pennsaid 2% pursuant to the "Hatch-Waxman Act".

The approval of Pennsaid 2% was for the pain of knee OA, as opposed to the treatment of the signs and symptoms of knee OA, which was the approved indication for Pennsaid. The lesser indication was granted because the Phase 2 study submitted to the FDA wasn't adequately powered as a pivotal study and therefore statistical significance was achived for the pain endpoint only. Statistical significance was not achieved for physical function and overall health assessment. These latter endpoints had been achieved in all Pennsaid Phase 3 studies resulting in the signs and symptoms indication, a much broader indication.

In April 2013, Nuvo delivered a formal notice of material breaches (NOMB) to Mallinckrodt that was intended to give Mallinckrodt an opportunity to cure the breaches alleged by Nuvo and served as a pre-condition to Nuvo commencing formal legal proceedings for breaches of the U.S. Licensing Agreement. On August 20, 2013, Nuvo commenced legal action against Mallinckrodt by filing a complaint in the U.S. District Court for the Southern District of New York. Nuvo is accusing Mallinckrodt of breaching the U.S. Licensing Agreement in which Nuvo licensed the right to sell and market Pennsaid® and Pennsaid® 2% in exchange for Mallinckrodt taking on certain obligations in relation to clinical development of Pennsaid® 2%.

Nuvo is asserting that Mallinckrodt breached the U.S. Licensing Agreement for Pennsaid® in the following ways:

- Mallinckrodt willfully failed to conduct two Phase 3 clinical trials that were agreed upon and required under the Pennsaid® U.S. Licensing Agreement. These trials are vital to 1) securing an indication and product label for Pennsaid® 2% in the U.S. that is equivalent to those for Pennsaid®; 2) providing evidence of robust efficacy of Pennsaid® 2% for marketing in the U.S. and throughout the world, and 3) obtaining regulatory approval for Pennsaid® 2% outside the U.S.
- Negligent errors in the clinical studies performed for Pennsaid® 2% by Mallinckrodt, specifically the failure to conduct proper pharmacokinetic studies, led to a delay of FDA's approval of Pennsaid® 2% in the U.S.
- Mallinckrodt has not put forth requisite sales efforts for Pennsaid® in the U.S., and this has resulted in significantly lower sales and royalties payable to Nuvo.
- Mallinckrodt has willfully refused to pay the full milestone payments due to Nuvo under the Pennsaid® U.S. Licensing Agreement.

Nuvo is seeking damages of at least $100 million along with the right to terminate the Pennsaid® U.S. Licensing Agreement that would result in Nuvo retaining all rights to market and sell Pennsaid® and Pennsaid® 2% in the U.S. While the case is being litigated, both companies are operating on the basis of the agreement set forth in the Licensing Agreement. Nuvo and Mallinckrodt have agreed to a joint discovery schedule in which document discovery is to be substantially completed by June 2014; all fact discovery is to be completed by December 2014. According to the current schedule, a trial would likely not occur until at least mid to late 2015.

…Topical NSAID Market Analysis…

The knee OA market represents a sizable population as it is estimated that 16% of Americans over the age of 45 have symptomatic knee OA (Jordan *et al*. 2007). According to the 2010 Census, there were approximately 121 million Americans over the age of 45. This puts the total knee OA target population at approximately 19 million individuals. Above we previously reported data from the U.S. CDC estimating approximately 27 million people in the United States who suffer from OA. Thus, we believe fair patient target population is between 20 and 25 million.

In the U.S. there are a number of products available for the treatment of OA including: over-the-counter (OTC) oral medications that are available without a prescription. These include acetaminophen and low-dose oral NSAIDs such as ibuprofen or naproxen. Prescription-only medications, such as full-strength NSAIDs (both with and without proton pump inhibitors), COX-2 selective NSAIDs, oral opiate analgesics, and topical NSAIDs are also available. We estimate that in 2012, topical NSAIDs captured 4 million prescriptions and the total size of the market exceeded $500 million in the U.S.

Pennsaid® is one of three topical NSAIDs approved by the FDA, with the others being Voltaren® Gel (diclofenac sodium topical gel) 1% sold by Endo Pharmaceuticals, and Flector® Patch (diclofenac epolamine patch) 1.3% sold by Pfizer.

- Voltaren® Gel: While being available in Europe for a number of years as Voltarol Emulgel (1.16% diclofenac diethylammonium), Voltaren® Gel was only first approved by the U.S. FDA for use in the U.S. in 2007. Clinical trial results showed that Voltaren® Gel was effective in treating OA of both the knee and hand as assessed by the WOMAC pain sub-index. According the IMS Health, the number of prescriptions written for Voltaren® Gel was 4,087,123 between Oct. 1, 2012 and Sep. 30, 2013. Net sales of Voltaren® Gel were $117.6 million and $170.8 million for the full years 2012 and 2013, respectively.

- Flector® Patch: The Flector® Patch was approved by the FDA in 2007 for the treatment of minor sprains, strains and contusions. It was originally developed by King Pharmaceuticals, which was acquired by Pfizer, Inc. in 2010. Net sales of the Flector® Patch were approximately $145 million and $160 million in 2010 and 2011, respectively.

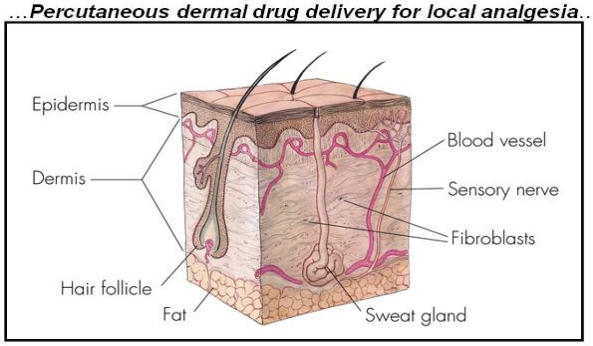
We expect generic competition to Pennsaid® will begin by the middle of 2014, thus we believe that Pennsaid® 2% will be the main driver of revenues for Nuvo in the knee OA market in the U.S. Pennsaid® 2% became available in the U.S. in February 2014 and we are modeling prescription growth similar to what was seen after the launch of original Pennsaid®. Nuvo is set to receive royalties of 20% on net sales of Pennsaid® 2%. Mallinckrodt's CEO, Mark Trudeau, has stated he expects Pennsaid® 2% to generate "tens of millions of dollars" in annual sales. Thus, we have modeled for Pennsaid® 2% to peak at approximately $75 million in annual sales. We discuss our valuation of Nuvo Research based on this forecast below.

HLT Patch (Synera®) and Pliaglis®

In May 2011, Nuvo acquired ZARS Pharma, Inc., a U.S. specialty pharmaceutical company focused on the development and commercialization of topically administered drugs, primarily with respect to pain. The ZARS acquisition significantly broadened Nuvo's pain pipeline by adding two approved products, Synera® (which Nuvo refers to as the HLT Patch) and Pliaglis®, a pipeline of pain products in various stages of development and two important drug delivery platforms, Controlled Heat Assisted Drug Delivery (CHADD™) and topical film-forming dosage forms (Peel and DuraPeel™).

Proper delivery of drugs through the skin is a complex process, as the skin is a very effective barrier against the transport of compounds into and out of the body. The skin is composed of the outermost epidermis, which is avascular, and the dermis, which is vascular and which contains the free nerve endings that are responsible for pain sensation, thus rendering the dermis as the target area for anesthetic action (see Figure to right). The superficial layer of the epidermis is the stratum corenum, which is almost impermeable and responsible for the barrier function of the skin. It presents a barrier to the absorption of drugs and is the rate-limiting step in the penetration process.

…Percutaneous dermal drug delivery for local analgesia…



Source: NIGMS

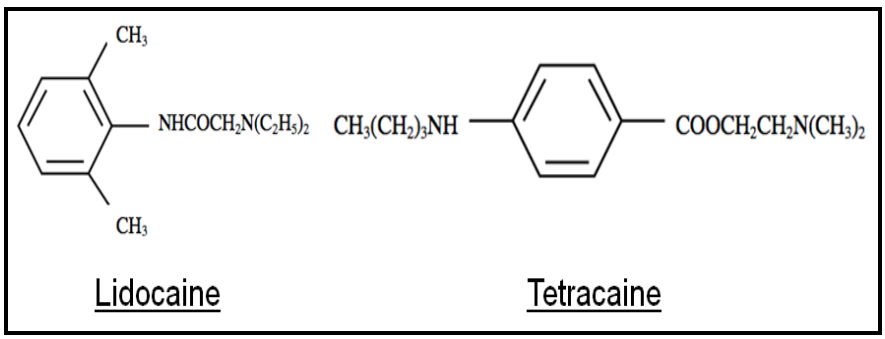
Drug penetration through the skin involves diffusion via transcellular and intercellular pathways, as well as through hair follicles and sweat glands. Transport depends on a range of factors including whether permeation is steady state or transient, the pKa of the drug (the pH at which the drug exists in both its non-ionic 'base' and ionic 'salt' states in equal proportions), the size of the drug compound, binding affinity, solubility, the integrity and thickness of the stratum corneum, the density of sweat glands and hair follicles, and how the drug is metabolized. The pKa of an anesthetic is important, as it is the base form of the drug that permeates the stratum corneum, thus the closer the pKa of the drug is to the pH of the vehicle and skin then the more drug is in a highly penetrable form.

Once penetrated through the stratum corneum, the anesthetic provides its pharmacologic effect by inhibiting the propagation of nerve impulses. This is accomplished by the base form of the drug by penetrating the axolemma, the outer nerve sheet, and blocking the influx of sodium ions into the nerve cell, thereby dampening the generation of action potential.

…Synera® licensed to Galen…

In July 2013, Nuvo sold the rights to market and sell Synera® in the U.S. to Galen U.S. Inc. for its current indication. Under the terms of the licensing agreement with Galen, the Synera® trademark was sold to Galen and Nuvo agreed to no long refer to the HLT Patch for other indications or other territories as Synera®.

Synera® (HLT Patch) is a topical patch using Nuvo's proprietary CHADD™ technology that combines lidocaine, tetracaine, and heat. The CHADD™ unit generates gentle heating of the skin and in a well-controlled clinical trial demonstrated that it contributes to the efficacy of Synera®. Synera® resembles a small adhesive bandage in appearance and is applied to the skin 20 to 30 minutes prior to painful medical procedures, such as venous access, blood draws, needle injections, and minor dermatologic surgical procedures (Figure 3).



The formulation of the unit is an emulsion in which the active ingredients are in an oil phase as a eutectic mixture containing 70 mg lidocaine and 70 mg of tetracaine in a 1:1 ratio by weight. The inactive ingredients are polyvinyl alcohol, sorbitan monopalmitate, water, methylparaben and propylparaben. The total surface area of Synera® is approximately 50 cm^2, of which the active area is 10 cm^2.

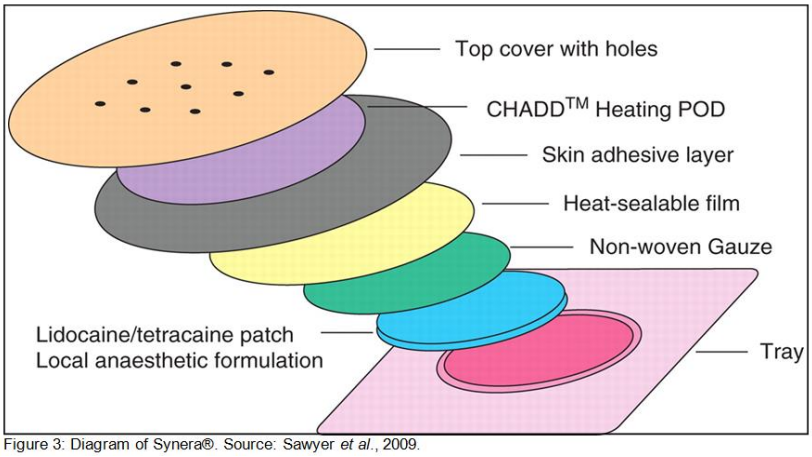


Figure 3: Diagram of Synera®. Source: Sawyer *et al*., 2009.

…Clinical Testing of Synera®…

There have been a large number of clinical studies performed with Synera®, as the product has been tested on over 1,000 patients. A sampling of the clinical trial results is presented below.

- A 2005 randomized, double-blind study published in Dermatologic Surgery compared Synera® with placebo in providing effective anesthesia before minor dermatological procedures such as skin tag removal, superficial excision, electrodessication, and shaved biopsies (Berman *et al*., 2005). The patient population consisted of adult patients and the patch was applied for 30 minutes prior to the procedure. The results showed that patient-reported pain intensity was significantly lower in the Synera® treated group ($P < 0.01$). Investigators and an independent observer rated the pain in the Synera® patch group to be less than in the placebo patch group ($P = 0.04$ and $P < 0.001$, respectively).

- Another randomized, double-blind study published in 2005 in Dermatologic Surgery examined a group of geriatric patients (n = 79, 65 years of age or older) who were treated with either Synera® patch or a placebo patch for 30 minutes prior to a shave biopsy or superficial excision (Shecter *et al*., 2005). The results showed a statistically significant difference in patient ratings of pain ($P = 0.041$) with less pain reported by those patients treated with Synera®.

- A study published in The Clinical Journal of Pain examined the depth of anesthesia due to Synera® compared with placebo in 12 healthy adult volunteers (Shomaker *et al*., 2000). After administration of the drug or placebo, the depth and duration of anesthesia were recorded at defined intervals between 10 and 120 minutes after treatment. Depth of anesthesia was determined with a 21-gauge short bevel needle attached to a depth gauge. Statistically significant differences in depth and duration of anesthesia were found between patients treated with Synera® and placebo. The depth of anesthesia was found to be 6.8 mm with Synera® and 4.7 mm with placebo with the anesthetic effect lasting for 120 minutes with Synera® compared to 10 minutes with placebo.

- A 2007 randomized, double-blind study published in Pain Medicine compared Synera® to placebo in adult volunteers (Curry *et al*., 2007). The patches were applied for 20 minutes before a vascular access procedure. The results of the study showed that more subjects reported adequate anesthesia with Synera® than placebo (73% vs. 31%, $P = 0.002$), with more subjects indicating they would use Synera® again (70% vs. 33%, $P = 0.006$).

…Synera® vs. EMLA…

Eutectic mixture of local anesthetics (EMLA) is an oil-in-water emulsion mixture of lidocaine (25 mg/mL) and prilocaine (25 mg/mL) that provides localized anesthesia when applied to the skin. The cream was developed by AstraZeneca and was approved by the FDA in 1993. EMLA is applied under occlusive dressings, such as a Band-aid™, which aids diffusion into the skin. The recommended application time is 1 hour prior to a procedure.

In 2009, a study was published in the British Journal of Anaesthesia that compared Synera® to EMLA Cream (Sawyer *et al*., 2009). Eighty-two volunteers were randomized to receive Synera® on one antecubital surface (inner portion of the forearm) and EMLA on the other for 10, 20, 30 or 60 min before a vascular access procedure. Skin reactions and adverse events were evaluated and test subjects then rated pain intensity using a 100 mm visual analogue scale (VAS).

The pain VAS is a continuous scale comprised of a horizontal or vertical line, usually 10 cm (100 mm) in length, anchored by two verbal descriptors, one for each symptom extreme. For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" (score of 100). The pain VAS is self-completed by the respondent, where they are asked to place a line perpendicular to the VAS line at the point that represents their pain intensity. Using a ruler, the score is determined by measuring the distance (in mm) on the 10-cm line between the "no pain" anchor and the patient's mark.

The results of this study showed that median VAS scores were significantly lower for patients receiving Synera® compared to those receiving EMLA Cream for all treatment durations less than 60 minutes (Figure 4). The median VAS scores were the same between Synera® and EMLA Cream at 60 min. In addition, subject evaluations of the study treatments indicated superior analgesic effect for Synera® compared to ELMA Cream after short treatment periods. Significantly more subjects in to 10, 20 and 30 min treatment groups indicated they would use Synera® again compared with EMLA Cream. Lastly, significantly more subjects in the 20 and 30 minute groups reported that Synera® eliminated pain, including 100% of patients in the 30 min treatment group, compared with EMLA Cream.

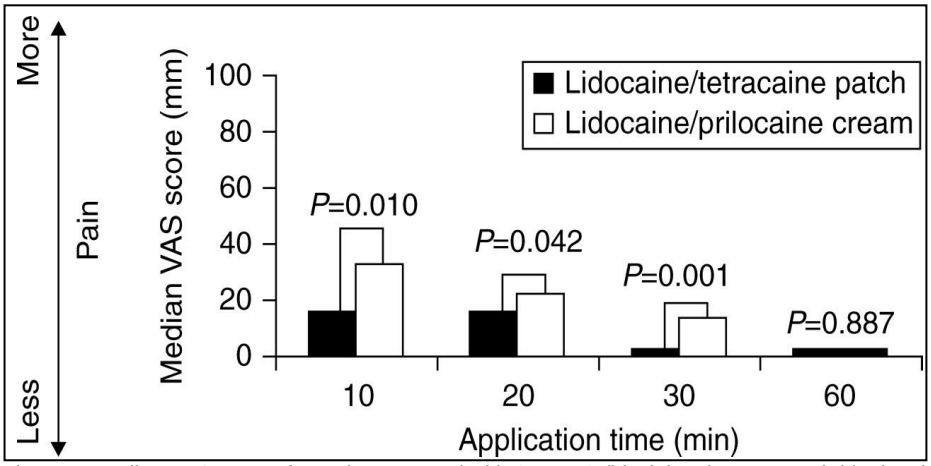


Figure 4: Median VAS scores for patients treated with Synera® (black bars) vs. EMLA (white bars).
Source: Sawyer *et al*., 2009.

Side effects were mild and both treatments were well tolerated. Synera® was associated with significantly more erythema than EMLA Cream at 20, 30 and 60 minute treatment times while EMLA Cream produced significantly more blanching than Synera® at 30 and 60 minutes. The only adverse event reported was nausea and faintness that occurred in two subjects; however, these were considered moderate in severity, unlikely related to the study treatments, and were most likely the result of the vascular access procedure.

…Synera® offers safe, effective dermal anesthesia…

Thus far, Synera® has proven to be a safe and effective option for providing localized dermal analgesia prior to a dermatological or vascular access procedure. Side effects associated with the use of Synera® include mild erythema, edema, blanching and burning sensation; however, all of these effects resolved spontaneously soon after treatment. We note there have been no systemic effects reported with the use of Synera® thus far. In several studies conducted in both adults and children, including those involving multiple patches, the plasma levels of lidocaine and tetracaine were well below toxic levels. Central nervous system toxicity is seen at levels approaching 5000 ng/mL, although early signs of toxicity can be evident at plasma levels of approximately 1000 ng/mL.

- Application of Synera® for 30 minutes in adults produced peak plasma concentrations of lidocaine less than 5 ng/mL with plasma levels of tetracaine below the limit of quantitation (< 0.9 ng/mL). Increasing the application time of the Synera® patch to 60 min did not significantly increase these values.

- Another study investigating systemic exposure following Synera® application involved the application of a) four successive Synera® patches for 30 minutes with a 30-minute interval between each patch application and b) three Synera® patches for 60 minutes each with a 60-minute interval between applications. The results showed that peak lidocaine plasma levels were 12 ng/mL for the 30-minute applications and 8 ng/mL for the 60-minute applications. There was no tetracaine detected in plasma following either treatment.

- A pharmacological study involving children showed that application of Synera® for up to 30 minutes in children 4 months to 12 years of age produced maximum peak plasma concentrations of lidocaine and tetracaine of 63 ng/mL and 65 ng/mL, respectively.

Given the immense amount of clinical data demonstrating that Synera® is both safe and effective, **WE CONCLUDE** that Synera® is a valuable asset for Nuvo, especially given the data showing it to work more quickly than AstraZeneca's EMLA Cream.

…Synera® commercial and licensing history…

Synera® is approved in the U.S. to provide local dermal analgesia for superficial venous access and superficial dermatological procedures, such as excision, electrodessication, and shave biopsy of skin lesions. In February 2012, Nuvo launched Synera® in the U.S., targeting interventional pain doctors with a small pain specialty contract sales organization (CSO). In August 2012, Nuvo refocused its resources on large national accounts such as dialysis centers, infusion centers, and blood diagnostic laboratories. To execute this strategy, Nuvo terminated its agreement with the CSO and used its internal commercial team to focus on these national accounts and the key interventional pain doctors who use Synera®.

In July 2013, Nuvo licensed the rights to market and sell Synera® in the U.S. to Galen U.S. Inc. for its current indication. Under the terms of the agreement, Galen made an upfront payment to Nuvo of U.S. $4.5 million on closing and Nuvo will receive royalties of 10% of net sales and is eligible to receive a U.S. $5.0 million milestone payment upon gross annual sales reaching U.S. $25.0 million and a further U.S. $5.0 million upon gross annual sales reaching U.S. $50.0 million.

In September 2012, Nuvo successfully completed a study to provide data to support an application for the removal of the "Not for Home Use by Patient" condition currently on the U.S. label of Synera®. The company filed a prior approval supplement (PAS) with the FDA in May 2013 requesting removal of the "Not for Home Use by Patient" condition from the label. On March 10, 2014 the FDA responded to the PAS by approving the request to have the "Not for Home Use by Patient" label removed.

In most E.U. countries, the HLT Patch is marketed under the trade name Rapydan® and it is approved for surface anesthesia of normal intact skin in connection with needle punctures in adults and children from 3 years of age, and for use in cases of superficial surgical procedures on normal intact skin in adults. Nuvo has licensed the sales and marketing rights to Eurocept International B.V. (Eurocept), a Dutch- based pharmaceutical company, for Western Europe, Russia and most of its former Republics, Turkey, Israel, and the People's Republic of China. Eurocept has responsibility for manufacturing and all commercialization activities and costs, including selling, marketing and medical education in the above countries. Under the terms of the agreement, Nuvo earns 15% royalties on the net sales of Rapydan® and is eligible to receive sales milestones. Rapydan® has not yet been approved in Russia and most of its former Republics, Turkey, Israel, and the People's Republic of China.

In May 2012, Nuvo entered into a license and supply agreement granting Paladin exclusive Canadian rights to market and sell the HLT Patch, upon regulatory approval. Under the terms of the agreement, Nuvo will receive a double-digit royalty on net sales in Canada and will supply the HLT Patch to Paladin. The HLT Patch has not yet been approved by Canadian regulatory authorities for marketing in Canada. Nuvo holds the sales and marketing rights for the HLT Patch in Mexico, South America, Australia, Africa and most regions in Asia, although it is not yet approved in any of these countries.

…Pliaglis®…

Pliaglis® is a topical local anesthetic cream that provides safe and effective local dermal analgesia on intact skin prior to superficial dermatological procedures, such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal. This product consists of a 1:1 eutectic mixture of 7% lidocaine and 7% tetracaine that utilizes the proprietary phase-changing topical cream Peel technology.

The Peel technology consists of a drug-containing cream that, once applied to a patient's skin, dries to form a pliable layer that releases drug into the skin. Pliaglis® is applied to intact skin for 20 to 30 minutes prior to superficial dermatological procedures and for 60 minutes prior to laser-assisted tattoo removal. Following the application period, Pliaglis forms a pliable layer that is easily removed from the skin allowing the dermatological procedure to be performed with minimal to no pain.

…Clinical testing of Pliaglis…

While Synera® is suitable for use on small, flat areas (such as injection sites or small biopsy areas), Pliaglis® has been used successfully and safely for topical anesthesia in a variety of dermatological procedures including the following:

- PDL Treatment: A 2002 study published in Dermatologic Surgery examined the clinical efficacy of Pliaglis® as a topical anesthetic for PDL treatment as well as to determine the optimal application time (Bryan *et al*., 2002). Sixty patients were enrolled in one of three separate double-blind, placebo-controlled protocols in which Pliaglis® or placebo was applied to the skin and left intact for 20, 30 or 60 minutes prior to laser treatment. Results showed that all patients experienced significant pain reduction with Pliaglis®. Patients receiving Pliaglis® for 60 minutes before therapy had a median VAS score of 8.0 mm compared with a median VAS score of 36.0 mm for patients receiving placebo ($P = 0.005$). An application time of 20 or 30 minutes was shown to be just as effective as 60 minutes in achieving anesthesia.

- Cryotherapy: A 2005 study comparing Pliaglis® to placebo for local anesthesia before cryotherapy was performed with 20 adult patients with facial actinic keratoses (Golderg, 2005). Patients received concurrent 30-minute applications of Pliaglis® and placebo, randomized to the top right or bottom left of the treatment surface. After removal of the drugs, cyrotherapy of the actinic keratosis with liquid nitrogen was performed. Results showed that Pliaglis® was more effective than placebo in relieving pain, with significantly lower VAS scores at the Pliaglis® sites than at the placebo sites (17 mm vs. 47 mm, $P = 0.002$).

- Collagen Injections: Pliaglis® was found to be significantly more effective than placebo for local anesthesia before collagen injections on the face (Armenakas *et al*., 2005). In a double-blind study, 52 patients received both Pliaglis® and placebo, applied concurrently and randomized to different matched skin treatment areas. After a 30-minute application time the collagen injections were performed. Results showed that Pliaglis® produced significantly lower median VAS scores than placebo (16.0 mm vs. 35.0 mm, $P < 0.001$).

- Laser-Assisted Hair Removal: A double-blind, placebo-controlled study of 50 adults receiving Pliaglis® or placebo showed that laser-assisted hair removal is more tolerable with application of Pliaglis® (Alster *et al*., 2005). After a 30-minute application, laser-assisted hair removal was performed with results showing Pliaglis® treatment produced lower median VAS scores compared with placebo (19.5 mm vs. 25.0 mm, $P = 0.017$).

- Nonablative Facial Resurfacing: A 2003 study published in Dermatologic Surgery examined the efficacy of Pliaglis® for use in nonablative facial laser resurfacing (Doshi *et al*., 2003). Twenty patients received concurrent 30-minute applications of Pliaglis® and placebo randomized to opposite cheeks in a double-blind fashion. A statistically significant difference in median VAS scores was reported between Pliaglis® treated sites and placebo (15 mm vs. 47 mm, $P < 0.001$).

- Laser Leg Vein Ablation: A randomized, double-blind, placebo-controlled study was published in 2004 in Lasers in Surgery and Medicine that evaluated the efficacy of Pliaglis® as a topical anesthetic for laser leg vein ablation (Jih *et al*., 2004). Study treatments were applied for 60 minutes prior to laser treatment of leg veins using a 1,064 nm long-pulsed laser. There was a statistically significant difference in VAS score for Pliaglis® sites versus placebo sites (27 mm vs. 43 mm, $P < 0.001$). Of note is that the longer-wavelength lasers, such as the one used in this study, have been associated with greater degrees of pain than conventional lasers and have been known to cause users to stop therapy due to pain.

- Laser-Assisted Tattoo Removal: This procedure is typically associated with a high degree of pain, thus warranting the use of a topical anesthetic. A 2005 study evaluated the efficacy of Pliaglis® before laser-assisted tattoo removal in a randomized, double-blind fashion (Chen *et al*., 2005). Thirty patients received Pliaglis® and placebo simultaneously for 60 minutes. Results showed significantly lower VAS scores at the Pliaglis® sites than at placebo sites (38.0 mm vs. 68.0 mm, $P = 0.001$).

…Pliaglis® is a safe and effective dermal anesthetic…

For all the studies, adverse events were mild in severity and limited to local skin reactions. The most common side effects were very similar to what was seen with studies involving Synera®, which were erythema, blanching and edema. Pharmacokinetic studies showed that the amount of lidocaine and tetracaine systemically absorbed from Pliaglis® is directly related to both the duration of application and the surface area over which it is applied. Application of Pliaglis® for 30, 60 and 90 minutes in areas measuring 50 to 200 cm^2 yielded peak plasma concentrations below the lower limit of quantitation for both lidocaine and tetracaine (100 ng/mL and 5 ng/mL). A second study showed that application of 59 g of Pliaglis over 400 cm^2 for up to 120 minutes produced a peak plasma concentration of lidocaine of 220 ng/mL, which is still only $1/20^{th}$ of the lowest concentration considered to be toxic.

Based on the plethora of clinical studies showing efficacy in a number of dermatological procedures with few adverse events, **WE CONCLUDE** that Pliaglis® is a safe and effective local anesthetic and is a valuable asset in Nuvo's portfolio.

…Pliaglis® commercial and licensing history…

Galderma Pharma S.A., a global pharmaceutical company specialized in dermatology, holds the worldwide sales and marketing rights for Pliaglis®. Under the terms of the licensing agreement, Nuvo earns royalties on the net sales of Pliaglis® and is eligible to receive milestone payments when certain specified approvals are obtained and launches occur.

Pliaglis® was initially approved by the FDA in June 2006, but was voluntarily removed from the U.S. market by Galderma in 2008 due to manufacturing issues at Galderma's third-party contract manufacturing organization. In December 2011, Galderma submitted an sNDA for Pliaglis® that addressed a number of manufacturing issues, including the transfer of manufacturing to Galderma. In April 2012, Galderma received a CRL from the FDA that outlined additional information the FDA required before it would approve the sNDA for Pliaglis®. In May 2012, Galderma submitted additional information that addressed the FDA's issues, and on October 18, 2012, the FDA approved the sNDA.

Galderma launched Pliaglis® in the U.S. in March 2013 at the American Academy of Dermatology Conference in Miami. Galderma launched Pliaglis® in the U.S. through a third-party distributor and in January 2014 it hired a small sales force to start marketing Pliaglis®.

In the E.U., the Marketing Authorization Application (MAA) for Pliaglis® that was prepared by Nuvo, as per its obligations under the terms of the licensing agreement, was validated in July 2012. The MAA was submitted using the decentralized procedure with Germany as the Reference Member State and filed with 16 countries as Concerned Member States. On May 6, 2012, the company received notice of a positive opinion from the European decentralized procedure for the approval of Pliaglis®. The positive opinion required a post approval commitment study, the cost of which will be shared equally by Galderma and Nuvo. Pursuant to Nuvo's license agreement with Galderma, Nuvo was entitled to receive milestone payments totaling U.S. $6.0 million when certain specified launches occur or within a predefined 6-month period after marketing approval in three different countries. Nuvo earned these milestones in 2012 and all payments have been received. Galderma launched Pliaglis® in the E.U. in April 2013 at the Anti-Aging Medicine World Congress & Medispa in Monaco.

In South America, under the terms of the licensing agreement, Nuvo was entitled to receive a milestone payment totaling U.S. $2.0 million when a certain specified launch occurred or within a predefined 6-month period after marketing approval in the second approved country in South America. In September 2013, Galderma received marketing approval in Brazil, entitling Nuvo to the U.S. $2.0 million milestone payment. Nuvo expects to receive this milestone payment in the first quarter of 2014. Galderma laucned in Brazil in March of 2014.

…Topical anesthetic market analysis…

Both Synera® and Pliaglis® face competition in all markets from other topically applied local anesthetic drugs including EMLA Cream, L.M.X. 4 and L.M.X. 5. EMLA Cream is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a 1:1 ratio (w/w). It is indicated as a topical anesthetic for use 1) on intact skin to provide local analgesia, 2) on genital mucous membranes for superficial minor surgery, and 3) as a pretreatment for infiltration anesthesia. The product is owned and sold globally by AstraZeneca, but is also available as a generic product. EMLA Cream is applied in a thick layer to intact skin and must be covered with an occlusive dressing.

Local dermal analgesia is achieved after approximately 60 to 120 minutes. EMLA Cream is also available in a patch form in multiple jurisdictions for needle punctures. It is used as a topical anesthetic and contains lidocaine 2.5% and prilocaine 2.5%. Sales of EMLA Cream on a global basis are over $100 million.

L.M.X.4 and L.M.X. 5 Anorectal Creams are topical anaesthetic creams containing 4% and 5% lidocaine. L.M.X.4 is indicated for the temporary relief of pain and itching due to: minor cuts, minor scrapes, minor burns, sunburn, minor skin irritations and insect bites. L.M.X.5 Anorectal Cream is approved for the temporary relief of local discomfort, including pain and itching and soreness or burning associated with anorectal disorders. The product is also used for cosmetic procedures such as waxing and laser hair removal. L.M.X. 4 and L.M.X.5 Anorectal Creams are OTC products marketed by Ferndale Laboratories, Inc. in the U.S.

Nuvo receives 10% royalties on sales of Synera® in the U.S. and 15% on sales in the E.U., which amounted to $143,000 in 2013. For Pliaglis®, Nuvo receives 16% royalties on sales in the U.S. and 13% in the E.U., which amounted to $118,000 in 2013. Pliaglis® was launched by Galderma in March 2013 without a sales force to actively distribute it. However, in early 2014, Galderma began promoting Pliaglis® with a small sales force, thus sales are likely to increase in the coming years. Nuvo began receiving royalties on U.S. net sales of Synera® in July 2013, when the company sold Synera® to Galen. We believe Synera® and Pliaglis® each have peak sales in the $10 to $20 million range, putting peak royalties to Nuvo Research in the $1 to $3 million range. We have incorporated these forecasts in our valuation model below.

WF10 and Oxoferin

WF10's pharmacological profile is best described as that of an immune-modulator with anti-inflammatory properties. Its clinical efficacy was shown in a recent randomized, placebo-controlled, double-blind parallel-group clinical trial where WF10 treatment led to a statistically-significant and clinically-relevant decrease of symptoms in patients with persistent allergic rhinitis. WF10 is believed to exert effects on macrophages and the mechanisms by which they modulate the immune response. WF10 is an aqueous solution (1:10 dilution) of the chlorite drug OXO-K993 (tetrachlorodecaoxide) that is given intravenously and has potential applications in immune modulation, adjuvant cancer therapy, immune deficiencies, and chronic viral infections. It is currently approved for use in Thailand under the name Immunokine® in patients with post-radiation chronic inflammatory disease including cystitis, proctitis, and mucositis. Recently Immunokine's label has been expanded to include treatment of diabetic foot ulcers. WF10 is currently being tested as a treatment for severe allergic rhinitis, a potential $10 billion market opportunity.

Oxoferin is a topical wound healing agent that is a diluted form of WF10 (1:5) with research to date suggesting it has a positive impact on wound healing and leads to contraction, closure and faster healing of wounds.

…Allergic rhinitis…



While previously considered a rare condition, recent epidemiological studies show that allergic rhinitis affects 40% of children and 10-30% of adults worldwide (>300 million people) (Steinsvaag, 2011).

The hallmark clinical manifestations of allergic rhinitis are nasal itching, sneezing, nasal running, and nasal obstruction. The condition is commonly regarded as merely a seasonal nuisance; however, it is associated with persistent mucosal inflammation (Ciprandi *et al*., 1995) that can hamper response to viral colds (Cirillo et al., 2007).

The term atopy refers to a syndrome whereby an individual develops an IgE mediated immune response to seemingly innocuous and ubiquitous environmental antigens. Atopic diseases include allergic rhinitis, rhino-conjunctivitis, asthma, atopic dermatitis, and food allergies. It is currently unclear why certain individuals develop allergies, but there appears to be both genetic and environmental influences in their etiology.

A host of risk factors are linked to allergic rhinitis, including high socioeconomic status, environmental pollution, being born during pollen season, having no older siblings, heavy maternal smoking during the first year of life, high concentrations of serum IgE (>100 IU/mL before age 6), and early introduction of foods or formula (Scadding et al., 2008). A number of studies have shown that exposure to different infectious agents, including hepatitis A, Mycobacterium, Toxoplasma gondii, or the products of these agents (e.g., endotoxins) protects against the development of atopic diseases (Mutius et al., 2010).

Allergic rhinitis is typically associated with other respiratory inflammatory diseases such as asthma, rhinosinusitis and allergic conjunctivitis. Rhinitis and asthma have a propensity to occur together, according to a number of epidemiological studies (Bousquet et al., 2001). There also appears to be a connection between sinus disease and allergic rhinitis with 25% of individuals with acute sinusitis having allergic rhinitis and approximately 50% of those with unilateral chronic sinusitis and up to 80% with chronic bilateral sinusitis (Fokkens et al., 2007). Eye symptoms are also seen in approximately 70% of individuals with seasonal allergic rhinitis and approximately 50% of those with perennial rhinitis (Canonica et al., 2007).

Rhinitis is classified as allergic, non-allergic, or occupational with 2/3rd of children and 1/3rd of adults presenting with allergic rhinitis (Scadding, 2001). The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines for classification define allergic rhinitis as either intermittent or persistent and mild or moderate-to-severe (Figure 5; Bousquet et al., 2008). Allergic rhinitis is mostly triggered by inhaled allergens such as grass pollen, tree pollen and dust mites (Bousquet, et al. 2007) In order to confirm a diagnosis of allergic rhinitis, specific IgE reactivity to airborne allergens needs to be performed through either hypersensitivity skin testing or a blood test.

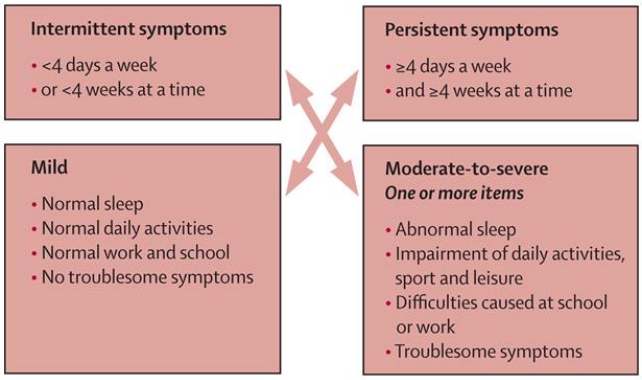


Figure 5: ARIA Classification of Allergic Rhinitis. *Source*: Greiner *et al.*, 2012

The pathogenesis of allergic rhinitis is initiated by an allergic response to inhaled antigens. For reasons that have yet to be elucidated, certain individuals will be sensitized to harmless antigens (such as tree pollen) via activation of dendritic cells and T lymphocytes. Dendritic cells are found at mucosal surfaces to capture allergens and act as antigen-presenting cells, thereby presenting the allergenic peptide to T lymphocytes in draining lymph nodes. CD4+ T lymphocytes play a key role in initiation of the allergic immune response through secretion of certain cytokines, particularly interleukin 4, which induces the IgE class switch in B lymphocytes thereby driving sensitization to allergens. The IgE molecules bind to high-affinity receptors on the surface of tissue mast cells and circulating basophils. When allergens bind to allergen-specific IgE on the surface of mast cells they induce the rapid release of preformed mediators such as histamine, leading to the symptoms typically associated with allergic rhinitis - sneezing, rhinorrhea and nasal itching.

…Current Treatment Options for Allergic Rhinitis…

Several treatment options exist for dealing with the symptoms of allergic rhinitis and they belong to a number of different classifications and can be administered either nasally or orally.

Topical Nasal Medications - Nasal application has the benefit of fewer side effects as a majority of the medicine stays in the nose and does not travel throughout the body.

- Corticosteroids: This class of compounds work by reducing the swelling and inflammation in the nose. Examples of nasal corticosteroids include fluticasone (Flonase®), mometasone (Nasonex®) and triamcinolone (Nasacort®). Side effects of nasal corticosteroids include burning, dryness or irritation inside the nose, an increase in sneezing and irritation of the throat.



- Antihistamines: These compounds work by blocking the action of histamine, which is responsible for inducing the symptoms of allergic rhinitis including sneezing, itching and runny nose. Nasally administered antihistamines typically begin to provide relief from symptoms in as little as 15-30 minutes. Examples of antihistamines include azelastine (Astelin®) and olopatadine (Patanase®). Side effects of antihistamines are generally mild and include drowsiness and dry mouth.



- Chromones: These medications work by inhibiting the release of histamine from mast cells. An example of a chromone for the treatment of allergic rhinitis is sodium cromoglicate (Nasalcrom®). While being a safe and effective treatment for the prevention of allergic rhinitis symptoms, chromones are typically used only as a second- or third-line treatment due to the need for multiple applications per day and their weak effect compared to other previously aforementioned medications.

- Anticholinergics: When sprayed directly into the nose, anticholinergics (such as ipratropium bromide; Atrovent®) work by decreasing secretions from the glands lining the nasal passage, thus alleviating runny nose associated with allergic rhinitis. Since these medications need to be applied two to three times a day they are not typically a first line treatment. Side effects are generally mild but may cause an excessively dry nose that could cause nosebleeds or irritation.

Oral Medications – oral medications typically have a greater number of side effects compared to nasal treatments due to traveling throughout the body.



- Antihistamines: So-called second-generation antihistamines are considered non-sedating antihistamines that compete with histamine for binding to the histamine receptor type 1 receptor site in blood vessels, the gastrointestinal tract and respiratory tract. Examples include cetirizine (Zyrtec®), fexofenadine (Allegra®), and loratadine (Claritin®). These compounds are all effective in controlling symptoms of allergic rhinitis but do not affect nasal congestion, thus they are typically available as combination products with a decongestant.

- Antileukotrienes: These compounds are leukotriene receptor antagonists that inhibit the cysteinyl leukotriene receptor, thereby selectively preventing the action of leukotrienes released by mast cells and eosinophils. An example is montelukast (Singulair®) that has been shown to produce modest improvements in allergic rhinitis symptoms; however, this drug is not effective in all individuals.

- Decongestants: Pseudoephedrine (Sudafed®) is effective at reducing nasal obstruction, however it does not treat other symptoms of allergic rhinitis so is typically used in combination with an antihistamine. Side effects include increased heart rate, blood pressure, insomnia and anxiety.

The treatments for allergic rhinitis listed above generated sales in excess of $12 billion in 2009. There are approximately 82 million individuals in the United States that suffer from allergic rhinitis, with approximately 10 million patients who do not get adequate relief from conventional products and who are eligible for an alternative therapy such as immunotherapy.

…Immunotherapy for the treatment of allergic rhinitis…

Patients that do not respond to traditional allergic rhinitis treatments are usually administered allergy shots (immunotherapy) as a way to induce immune system tolerance to whatever allergen is inducing the symptoms. Treatment commences with a skin test to determine to which allergen(s) a patient is sensitized. The allergy shots themselves are a saline solution that contains a small amount of the allergen. Shots are administered once or twice per week with the amount of allergen in each shot increased gradually over time for the first 4 to 6 months. At this point, the patient typically enters the maintenance phase where the amount of allergen is kept constant and the frequency of shots is reduced to once every 2-3 weeks.

The patient continues on the maintenance phase for an additional 4 to 6 months, at which point their doctor will determine whether their reaction to the antigen has improved or worsened. If the symptoms have not improved the allergy shots are usually discontinued. An improvement of symptoms will result in a continuation of the shots for an additional 3 to 5 years. Allergy shots have been shown to be effective in treating both allergic rhinitis and allergic asthma. The length of time that they work after discontinuation of treatment varies from patient to patient, with some individuals never suffering from symptoms again while others have symptoms return after a couple of years.

…WF10 for the treatment of allergic rhinitis…

Given its ability to modulate the immune system, alter macrophage function, and its safe track record, Nuvo scientists explored the idea of whether WF10 could alter the immune response in allergic rhinitis. They conducted a Phase 2 randomized, double-blind, placebo-controlled, single-center trial to assess the efficacy and safety of WF10 infusions in 60 patients with at least a two year history of allergic rhinitis and a positive allergen skin test. In support of this, a 2012 study published in Microbiology and Immunology by scientists in Japan examined the role of macrophages in the initiation of allergic rhinitis in mice. Results showed that it was the submandibular lymph nodes that were the responsive organ to allergen challenge, with macrophages controlling both interleukin 4 production and class switching of immunoglobulin in lymphocytes – two processes that are responsible for the allergic response.

The primary end point of the Nuvo Phase 2 study was Total Nasal Symptom Score (TNSS). TNSS is the sum of the individual scores assigned by patients for sneezing, rhinorrhea, congestion, and nasal itching. WF10 was administered for five consecutive days at the start of the trial. The patients received no additional WF10 treatment and were followed for 12 weeks. Figure 6 shows the improvement in TNSS was much greater for WF10 treated patients than for placebo treated patients ($P < 0.001$). In addition, the improvement due to WF10 over placebo was already highly significant at week 3 and the difference between the groups was observed to last for the entire 12 week study period. While there was a decrease noted in TNSS for patients receiving placebo, this was not all that unexpected due to the fact that 1) any trial that uses a subjective endpoint is going to have a placebo response and 2) any trial involving drugs delivered intravenously (IV) will have a placebo response because patients think that a drug delivered IV is a stronger drug.

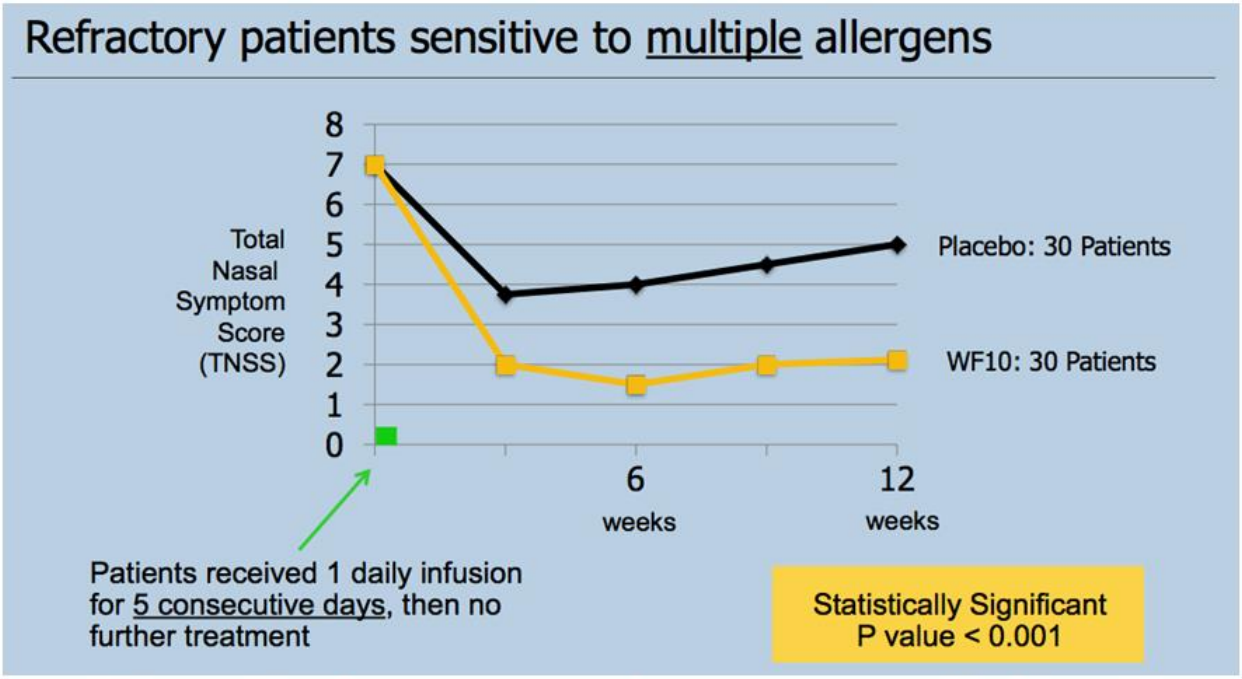


Figure 6: Data from a Phase 2 study showing a statistically significant decrease in Total Nasal Symptom Score (TNSS) for WF10 treated patients compared to placebo treated patients. *Source*: Nuvo Research, Inc.

A review published in 2010 summarized the clinical efficacy seen in treating allergic rhinitis with the different treatment classes: antihistamines, intranasal steroids (INSs), leukotriene receptor antagonists (LTRAs), and cromolyn sodium. The analysis utilized 54 randomized, placebo-controlled studies examining more than 14,000 adults and 1,580 children. While not a direct head-to-head comparison, Figure 7 below summarizes the results of the analysis and suggests that response to WF10 may be greater than response to any of the other class of allergic rhinitis treatments.

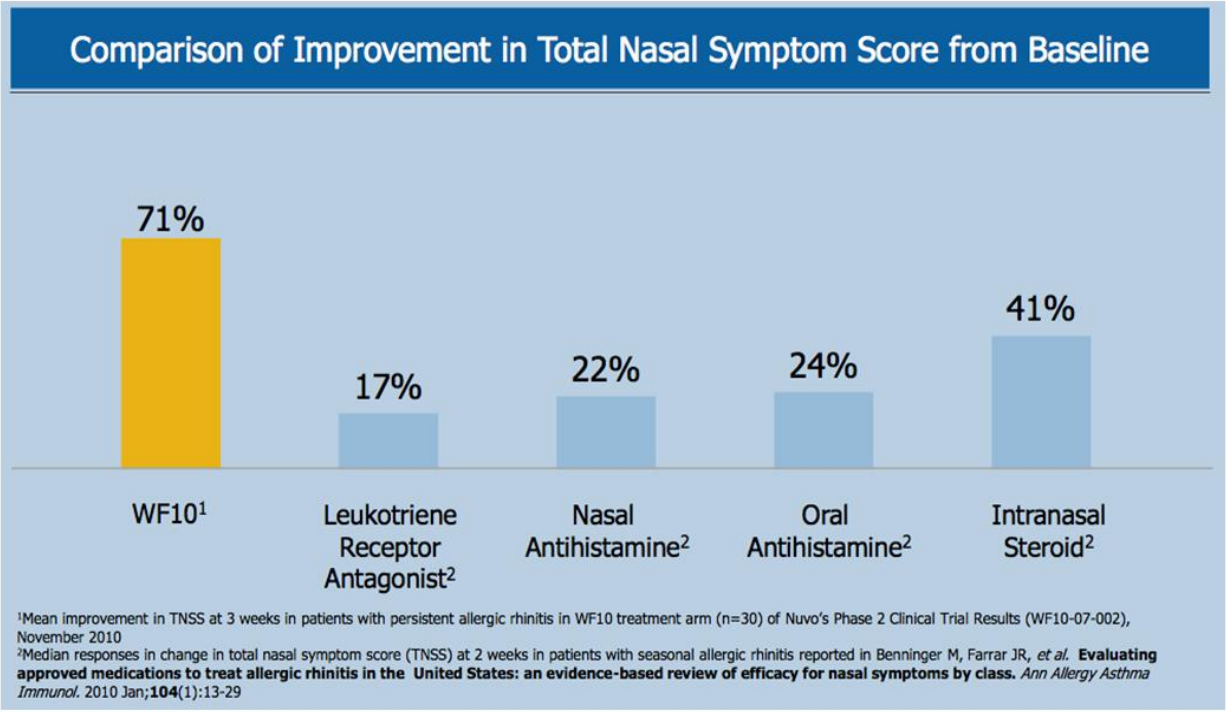


Figure 7: Comparison of treatment effects for different classes of allergic rhinitis treatments. *Source*: Nuvo Research, Inc.

In addition, Nuvo clinical research supports a number of potential label advantages that WF10 holds over immunotherapy treatment for allergic rhinitis. These include:

- It covers a broad range of allergens. The patients in the Phase 2 trial were all sensitized to multiple antigens. Immunotherapy treatment only targets a single allergen.

- Five days of treatment may provide relief for 1-2 years. In the Phase 2 trial, patients were treated once daily for five consecutive days and then not treated again for the duration of the study. For immunotherapy, patients must repeatedly be treated, typically every week for an extended period of time.

- A favorable safety profile, with no SAEs seen in the Phase 2 trial. Immunotherapy is generally well-tolerated, but there are possible rare serious side effects such as anaphylactic shock that could lead to death.

- A significant clinical benefit. The results of the Phase 2 trial showed that there was a response rate of 70-90%. For immunotherapy, there is typically a modest clinical benefit that takes a long time to manifest itself.

…WF10 vs. Circassia…

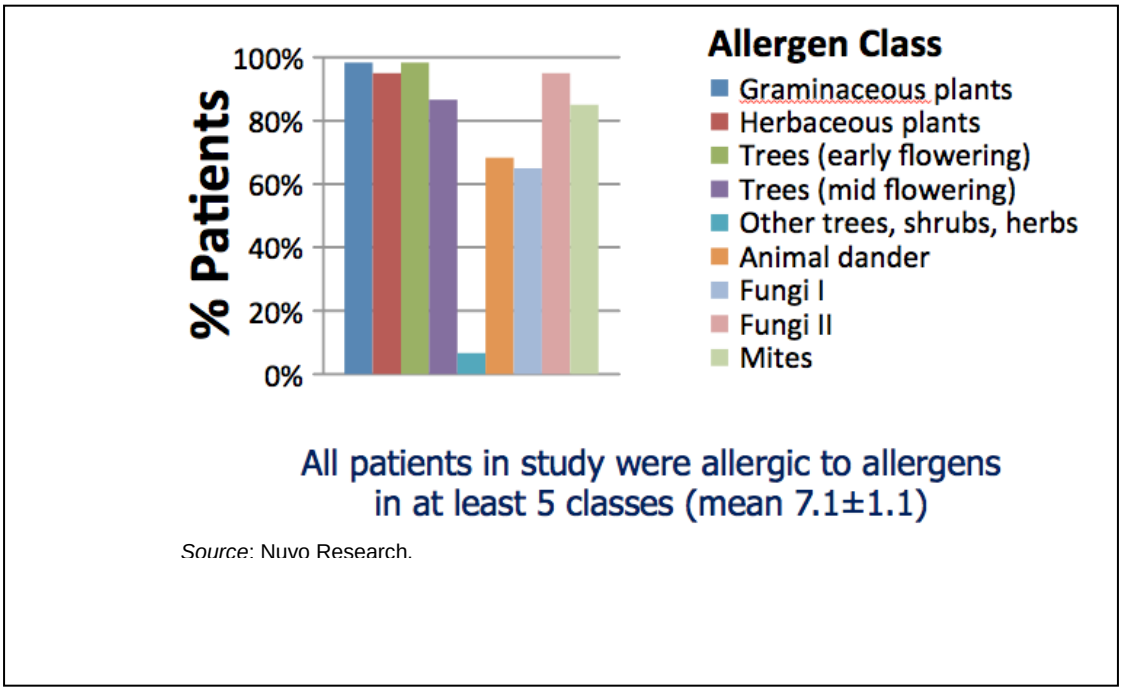
Circassia is a clinical-stage specialty biopharmaceutical company focused on the development and commercialization of a range of immunotherapy products for the treatment of allergies. The products were developed using the company's ToleroMune® technology. Using this technology, Circassia has developed a series of synthetic peptide immune-regulatory epitopes (SPIREs) that work to inhibit the cells involved in triggering the allergic response.

Thus far, clinical studies conducted by Circassia have demonstrated effective control of allergic symptoms with a short course of treatment (either four or eight injections over a three month time span) with minimal side-effects and long-lasting benefit. Circassia's lead product is Cat-SPIRE, developed for the treatment of cat allergies, and is currently in an ongoing Phase 3 registration study with results expected to be available in the first half of 2016. Clinical studies conducted thus far with Cat-SPIRE show that administration over a three month period is associated with a clinically significant mean reduction in allergic symptoms as measured by Total Rhinoconjuctivitis Score (TRSS, a widely used scoring system to track the severity of symptoms of rhinoconjuctivitis in clinical studies). The treatment effect appears to last for two years after treatment.

There are a number of similarities and some important differences between WF10 and Circassia's Cat-SPIRE treatment, which are indicated below.

	Cat-PAD (Circassia)	WF10 (Nuvo)
Indication	• Allergies symptoms	• Allergies symptoms
Allergen	• Cat dander	• Airborne allergens
Mode of administration	• 4 injections over 12 weeks	• 5 infusions over 5 consecutive days
Treatment effect duration	• 2 years	• Up to 2 years
Completed studies	• Phase II	• Phase II
Allergen exposure in clinical studies	• Environmental exposure chamber (EEC)	• Field study
Primary Symptom score	• TRSS (total rhinoconjunctivitis symptom score)	• TNSS (total nasal symptom score) • TOSS (total ocular symptom score)
Efficacy	• Statistically significant improvement in TRSS	• Statistically significanct improvement on TNSS and TOSS
Adverse events	• Headache • Similar safety profile to placebo	• Injection site reactions

While both technologies are used to treat allergies, Circassia's treatments are each unique to one particular allergen, thus they have treatments available for cat allergy, dust mite allergy, grass allergy, and ragweed allergy. Each treatment must be taken separately if a patient suffers from multiple allergies. This is in comparison to WF10, which can be utilized to treat a range of allergens, as shown below from the Phase 2 patient profiles whereby each of the patients in that study were allergic to allergens in at least five classes.



Source: Nuvo Research.

Innovative allergy immunotherapy treatments are beginning to attract substantial investor attention, with Circassia recently completing the largest biotech IPO in UK history where they raised £200 million ($335 million with an approximately $1 billion market cap). Clearly there is an intense interest in allergy immunotherapies that treat the underlying problems rather than just alleviating allergic symptoms, which WF10 has the potential to tap into.

…WF10 development plans…

Nuvo is planning to initiate a second Phase 2 trial of WF10 for the treatment of allergic rhinitis in the first half of 2014. The study will be a 160-subject, randomized, double-blind, placebo-controlled, 4-arm, multi-center trial to assess the safety and efficacy of five consecutive daily infusions of WF10 and its component ions versus a control. The last patient is expected to be dosed in the third quarter of 2014 with study results available by the end of 2014. In July of 2012 Nuvo secured up to €4.4 million of funding from the Development Bank of Saxony (SAB) for the further development of WF10 as a treatment for allergic rhinitis and other diseases. The funding will take the form of a non-repayable reimbursement of specific development monies expended by the company until July 2014. Nuvo has certain contractual obligations related to SAB, including the obligation to provide matching funding from its own resources of €1.9 million over the two-year period ending in July 2014.

…Oxoferin…

Oxoferin is a diluted form of WF10 that is used as a topical wound healing agent and is marketed by Nuvo Manufacturing GmbH in parts of Europe, and its partners in Asia and South America under several trade names including Oxoferin and Oxovasin.

Chronic wounds are caused by such conditions as burns, pressure sores, and poor circulation in the lower extremities. Comorbid conditions, which include diabetes and atherosclerosis, result in less blood flow to extremities and also increase the risk of developing chronic wounds such as diabetic foot ulcers and venous ulcers. Unlike acute wounds that pursue a normal course of healing, chronic wounds may persist for months or even years. Chronic wounds have a significant impact on the quality of life of patients and their caregivers, as well as healthcare system as a whole (Kane, 2008). Examples of chronic wounds include:

- Venous Leg Ulcers (VLUs): These types of ulcers, also known as stasis ulcers, occur due to improper functioning of venous values in the legs. An estimated 70-90% of venous leg ulcers become chronic (Snyder, 2005). In VLUs, edema and fibrinous exudate leads to fibrosis of subcutaneous tissues with localized pigment loss and dilation of capillary loops. There are an estimated 2.5 million VLU's treated in the U.S. each year.

- Diabetic Foot Ulcers (DFUs): These wounds are a major complication of diabetes, occurring in roughly 15% of all diabetics in the U.S. DFUs account for 84% of all lower leg amputations (Brem, 2007), and incidence corresponds to a major increase in mortality due to the development of macro and micro vascular complications. DFUs are caused by decreased sensation in the feet of diabetics resulting from deterioration of nerve endings affected by prolonged hyperglycemia. Inflammation resulting from diabetes also impedes the formation of granulation tissue and stalls wound healing. There are an estimated 1.5 million DFU's treated in the U.S. each year.

- Pressure Ulcers: These types of ulcers, also known as decubitus ulcers or "bedsores", are localized injuries to the skin and/or underlying tissue that usually occur over a bony prominence as a result of pressure, or pressure in combination with shear and/or friction. The most common sites are the sacrum, coccyx, heels or the hips, but other sites such as the elbows, knees, ankles or the back of the cranium can be affected. Pressure ulcers occur due to pressure applied to soft tissue resulting in completely or partially obstructed blood flow to the soft tissue. There are an estimated 2.0 million pressure ulcers treated in the U.S. each year.

Sales of WF10 and Oxoferin were $0.6 million in 2013. We do not forecast sales to increase significantly as all the patents associated with Oxoferin have expired.

Intellectual Property

The original composition patents for Pennsaid® have expired; however, Nuvo has patents that cover methods of using Pennsaid® including U.S. Patent Nos. 8,217,078; 8,546,450; and 8,618,164 that have expiry dates of 2029 and 2030. Nuvo also has various patents that cover the intellectual property surrounding Pennsaid® 2%. U.S. Patent No. 8,252,838 relates to the composition and methods of using Pennsaid® 2% and has an expiry date of April 2028. A further patent, U.S. Patent No. 8,563,613, has an expiry date of Oct. 2027. Nuvo received European Patent No. 2086504 that provides protection in the E.U. for the Pennsaid® 2% formulation and use.

Nuvo has a number of patents that cover Synera® that pertain to methods of manufacture and methods of use. One such patent family has the latest date of expiry as 2015. However, in 2012 the U.S. Patent Office reinstated U.S. Patent No. 6,465,709 that has an expiry date of 2020. In addition, two patent families directed to the use of Synera® are currently pending with expiry dates of 2030 and 2031 upon grant.

Pliaglis® is covered by two U.S. patents, 5,919,479 and 6,528,086, that have expiry dates of 2015 and 2020, respectively. These patents include claims that are directed at compositions of matter and methods of use.

Nuvo has two patents issued for the use of WF10 in treating allergic rhinitis. US Patents 8,252,343 and 8,435,568 cover the use of WF10 for treating allergic asthma, allergic rhinitis, and atopic dermatitis and have expiry dates of 2029 and 2028, respectively.

Technology and Pipeline

Nuvo has four proprietary topical and transdermal drug delivery (TTDD) platforms:

- Multiplexed molecular penetration enhancers (MMPE™): This patented technology uses combinations of molecular penetration enhancers (MPE) to permeate the skin to enhance delivery of drugs. As discussed earlier, the absorption of drugs through the skin is controlled by the stratum corneum. The MPEs interact with the stratum corneum to enhance its permeability, and Nuvo believes that a proprietary mixture of MPEs is the most effective way to maximize permeability.

- Controlled Heat Assisted Drug Delivery (CHADD™): CHADD utilizes a new technology to deliver controlled heat to enhance transdermal drug delivery. Heat is generated from a proprietary mixture of iron powder, activated carbon, sodium chloride, wood flour and water. This mixture is placed in a patch made of filter paper that is then sealed between two polymer films. One of the films has holes of pre-calculated size to allow air to penetrate while the heat generating chemical components are covered with an additional membrane with tiny holes. Exposure to the atmosphere allows air to flow through the holes at a controlled rate, igniting a chemical reaction that generates heat. The number and size of the holes can be altered to change the amount of heat generated and the duration of the reaction. The CHADD technology allows for more effective dosing, faster onset of action and reduced side effects.

- Peel and DuraPeel™: These technologies allow drugs to be delivered as a cream that dries to form a pliable self-occluding film. In one embodiment the cream is includes anesthetic agent(s) as active ingredients (lidocaine and tetracaine in the case of Pliaglis), a non-cross-linked cross-linkable agent, a plasticizing agent (to allow the cream to become a soft, flexible solid rather than a rigid one), an emulsifying agent, water absorbent polymers (to control water loss and retention) and water. The recommended application time of Pliaglis is 30 minutes, and once the application is complete the soft, pliable membrane that forms can be easily removed. Pliaglis can anesthetize large and irregular surface areas and results in a rapid onset of anesthesia. Other advantages of the Peel and DuraPeel technologies are that the membrane cannot be easily rubbed off and it conforms to the skin topography The difference between Peel and DuraPeel is that the Peel technology is utilized for short-term drug delivery while DuraPeel offers predictable drug delivery for up to 12 hours.

Nuvo has a large number of development stage products that the Company is actively seeking co-development and licensing partners for to advance in the clinic:

- ✓ HLT Patch for the treatment of acute musculoskeletal pain
- ✓ Flexicaine, an improved formulation of Pliaglis
- ✓ Triamcinolone Acetonide DuraPeel for the treatment of hand dermatitis
- ✓ Alprazolam patch for the treatment of anxiety disorder
- ✓ Ropivacaine DuraPeel for the treatment of neuropathic pain
- ✓ Testosterone DuraPeel for use as a male hormone replacement therapy
- ✓ Risperidone patch for the treatment of schizophrenia
- ✓ Topical antifungal for the treatment of onychomycosis

Nuvo Research Pipeline



Source: Nuvo Research, Inc.

VALUATION AND RECOMMENDATION

We are initiating coverage of Nuvo Research, Inc. (T.NRI) with a Buy rating with a price target of $7.50.

Our valuation is built upon the four FDA approved compounds as well as the potential for WF10 as a treatment for allergic rhinitis. When considering only the currently approved compounds, Nuvo is selling at a significant discount to even our conservative sales estimates. So, in essence, buying Nuvo today means an investor gets a piece of a specialty pharmaceutical company with a potential blockbuster allergy treatment for free. If WF10 proves to be successful in the treatment of allergic rhinitis, Nuvo has tremendous upside potential.

Pennsaid® 2% will look to gain market share in a $500 million topical analgesic market for OA

Pennsaid® 2% has a number of advantages over Pennsaid®, which we believe will lead to increased sales. These advantages include:

- Twice daily application instead of four times daily: Nuvo's data showed that patient compliance was likely part of the reason why Pennsaid® never gained a significant market share, as most patients did not apply Pennsaid® four times a day. Thus, they and their treating physicians were likely turned off by seemingly inferior efficacy. Twice daily dosing is likely to lead to far more compliance and thus make Pennsaid® 2% much more competitive with Voltaren® Gel.
- Improved delivery: Pennsaid® 2% is a more "gel-like" product, similar to Purell hand sanitizer. It goes on smooth, with no mess, and it dries very quickly. This is in comparison to Pennsaid®, which was more water-like with patients having to apply drop-wise onto their knees or onto their hand and then rub on to their knee. In addition, Pennsaid® 2% is supplied in a metered-dose pump bottle to aid patients in determining the proper dosage amount.

We model Pennsaid® sales to slowly decline as Pennsaid® 2% sales increase, with Pennsaid® eventually being removed from the market. We forecast peak Pennsaid® 2% sales of $75 million, and as Nuvo is set to receive 20% royalties on sales of Pennsaid® 2% we forecast peak royalties for Nuvo of approximately $15 million.

NPV ➔ Under this scenario, we believe that Pennsaid®/Pennsaid® 2% are worth: $45 million.

We forecast Synera® and Pliaglis® sales to increase in the future

Pliaglis® was launched by Galderma in March 2013 without a sales force to actively distribute it. However, in early 2014, Galderma began promoting Pliaglis® with a small sales force, thus sales are likely to increase in the coming years. Nuvo began receiving royalties on U.S. net sales of Synera® in July 2013, when the company sold Synera® to Galen. We believe Synera® and Pliaglis® each have peak sales in the $10 to $20 million range, putting peak royalties to Nuvo Research in the $1 to $3 million range.

NPV ➔ Under this scenario, we believe that Synera®/Pliaglis® are worth: $8 million.

WF10 is the wild-card in a potential $10 billion market

The Phase 2 data for WF10 in allergic rhinitis showed it to be more effective than placebo after just five days of treatment, with the therapeutic effect potentially lasting for 1-2 years. We forecast the current Phase 2 trial to be completed by the end of 2014, with a Phase 3 trial completed during 2016, an NDA filed in 2017, and approval occurring in 2018. We forecast the treatment to cost $1,000 and for WF10 to get approximately 10% of the market for patients needing immunotherapy treatment.

We believe that Nuvo will partner the drug, and could be in a position to do so with successful results from the current Phase 2 trial. We forecast a deal to be worth approximately $30 million in upfront/regulatory milestones with backend milestone payments of another $30 million with an estimated royalty rate of 12%.

NPV ➔ Under this scenario, we believe that WF10 for allergic rhinitis is worth: $31 million.

Nuvo Research: Sum-of-Parts Analysis	
Pennsaid/Pennsaid 2%	$45 million
Synera/Pliaglis	$8 million
WF10 Allergic Rhinitis	$31 million
WF10/Oxoferrin	$2 million
Cash & Investments	$14 million
Operating Burn	($10 million)
Total Firm Value	$90 million
Fully Diluted Shares	11.9 million[A]
Target Price	~$7.50/Share

A = Includes Basic Shares + all outstanding stock options and warrants

Potential risks to our thesis

The potential risks for investing in Nuvo at this stage involve the following:

- Pennsaid® 2% sales do not rise to our expectations
  Given the lackluster sales of Pennsaid®, it is not inconceivable that Pennsaid® 2% will not be well received by patients and physicians, which could have a detrimental effect on sales numbers. We believe this risk is mitigated by the advantages that Pennsaid® 2% has over Pennsaid®, however whether this will be enough to drive sales numbers to the level that we predict is uncertain.

- Synera® and Pliaglis® sales do not increase as forecast
  Thus far, sales of both Synera® and Pliaglis® have been quite small, although beginning in 2014 Pliaglis is now being marketed by a small sales force, which should help to increase sales. However, there is no guarantee that sales of these drugs will increase to the level that we predict, and while they are not the main drivers of the stock, the failure to achieve higher sales numbers from these products could have a negative effect on the share price.

- WF10 fails in clinical trials for allergic rhinitis
  This is perhaps the largest risk to an investment in Nuvo at this juncture. We have calculated a fair value for the company at approximately $90 million, with close to 1/3rd of that value derived from a probability-adjusted net present value calculation on WF10. The failure of WF10 would have a decidedly negative impact on the shares, and while the above-mentioned products are nice secondary drivers for the stock, removing WF10 from the investment story would cause us to significantly lower our price target.

- A poor outcome to the Mallinckrodt lawsuit
  Nuvo is confident that they have a very strong case against Mallinckrodt, and we believe that a settlement is likely to occur either at the end of 2014 or the first half of 2015. However, there is no guarantee as to what that settlement would include. Thus, two scenarios that would not be favorable to Nuvo include 1) reacquiring the rights to Pennsaid® and Pennsaid® 2% but then being unable to find a new partner to market the compounds and 2) not being monetarily compensated to perform the two Phase 3 trials necessary to get Pennsaid® 2%

approved outside the United States. In addition, if this case were to go to trial, there is no way to estimate what the outcome of the trial would be, which in turn could make the stock unattractive to most investors.

MANAGEMENT PROFILES

Daniel N. Chicoine, CPA – Chairman and Co-Chief Executive Officer
Mr. Chicoine has served as Nuvo's Chairman and has been actively involved in its day-to-day operations since 2004. Currently, he oversees the business development and strategic planning functions at Nuvo. From 2001-2004, Mr. Chicoine served as the Chief Financial Officer at Cosma International, Magna's body and chassis systems group. Mr. Chicoine served as the President of PowerCart Systems Inc., a Markham-based private company that designs and manufactures battery-equipped workstations that power devices with wireless communication capability. In 1997, Mr. Chicoine co-founded Nighthawk Investments, a private venture capital investment firm. In May 1994, Mr. Chicoine formed Triam Automotive Inc., an automotive parts supplier, with other former executives of Magna and, in July 1994, was instrumental in assisting the company complete its initial public offering. While at Triam, he served as Vice Chairman in charge of sales. From 1982 to 1993, Mr. Chicoine held various positions at the Magna group of companies, including President and CEO of Atoma International Inc. Mr. Chicoine is a graduate of the University of Toronto in commerce and is a Chartered Professional Accountant by profession.

John C. London, LLB, LLM – President and Co-Chief Executive Officer
Mr. London has over 30 years of experience managing a wide variety of public and private businesses. In his role at Nuvo, he oversees investor relations and legal departments and is actively involved in company strategic planning. Prior to joining Nuvo, Mr. London was President and Chief Executive Officer of Powercart Systems Inc. from 2002 to 2005, a Markham-based private company that designs and manufactures battery-equipped workstations that power devices with wireless communication capability. In 1997 Mr. London co-founded Nighthawk Investments, a private venture capital investment firm. In 1994, Mr. London formed Triam Automotive Inc., an automotive parts supplier, with other former executives of Magna International Inc., where he served as Executive Vice-President. Triam completed its initial public offering in 1994 and was sold to Magna in 1998. In 1988, Mr. London joined Magna International Inc., one of the world's largest automotive parts suppliers. From 1988 to 1993, he was Executive Vice-President, Secretary and General Counsel at Atoma International, Magna's interior systems group. Prior to joining Magna, Mr. London was a partner with the Toronto law firm of Strathy, Archibald and Seagram (now Gowlings) where he practiced corporate commercial law from 1981 to 1988. Mr. London is a graduate of the University of Western Ontario law school and holds a Masters of Law Degree from University College London.

Dr. Henrich R.K. Guntermann, MD, MSc – President, Europe & Immunology Group
Dr. Guntermann has more than 15 years of experience in the life sciences sector (including business development, restructuring and corporate financing). In his current role at Nuvo, Dr. Guntermann oversees the European operations and the Immunology Group. He previously held the position of President & Chief Executive Officer of Nuvo from 2004 to 2009. Prior to joining Nuvo, Dr. Guntermann, along with a group of distinguished life sciences entrepreneurs, founded BioAlliance AG, a German- based life sciences private equity and consulting firm. BioAlliance AG was formed to capitalize on the early stage development of the life sciences industry in the European Union by assisting life sciences companies find synergies and partnerships worldwide. Through its established international network, it brings together life sciences companies in the United States, Asia and Europe to foster growth through alliances. Dr. Guntermann received his medical doctorate at the Philipps-University in Marburg, Germany. He also received a Masters of Science in Biology, with specialization in pharmacology/toxicology and human genetics.

Stephen L. Lemieux, BA, MMPA, CPA – Vice President & Chief Financial Officer
Mr. Lemieux has over 10 years of public company experience. In his role at Nuvo, Mr. Lemieux oversees all of Nuvo's financial operations and is responsible for information technology, manufacturing, human resources and planning. Prior to joining Nuvo in 2007, Mr. Lemieux was the Corporate Controller at Martinrea International Inc., a publicly traded company listed on the TMX. Mr. Lemieux was responsible for financial reporting and the financial integration of an acquisition that increased revenues from $872 million to $2.0 billion. Prior to joining Martinrea, Mr. Lemieux was the Assistant Controller at Magna Powertrain (formerly Tesma International Inc.) (Tesma) and had previously held the position of Manager, Global Financial Reporting. Tesma was a public company listed on the TSX and NASDAQ, until it completed a "going private" transaction with Magna International Inc. in 2005. Prior to joining Tesma, Mr. Lemieux worked for Ernst & Young LLP performing audit, restructuring and accounting work for its clients. Mr. Lemieux is a Chartered Professional Accountant and holds a Master of Management & Professional Accounting from the University of Toronto.

Tina K. Loucaides, MSc, LLB – Vice President, Secretary & General Counsel
Ms. Loucaides has over 10 years of legal experience in the biotechnology and pharmaceuticals area. In her role at Nuvo, she is responsible for a wide range of legal and regulatory areas, including intellectual property, licensing, acquisitions, litigation, regulatory law and compliance. She joined Nuvo in 2008 as the company's Intellectual Property counsel. Prior to joining Nuvo, Ms. Loucaides was an associate lawyer with Bereskin & Parr in Toronto. As a member of the firm's biotechnology and pharmaceutical practice group, she advised clients on patents, licensing and litigation matters. Ms. Loucaides is a graduate of Osgoode Hall Law School and holds a Bachelor degree and a Master of Science degree from the University of Toronto specializing in immunology. Her Master's thesis focused on a co-stimulatory molecule involved in T cell activation. She is a registered Patent Agent in Canada and the United States.

PROJECTED FINANCIALS

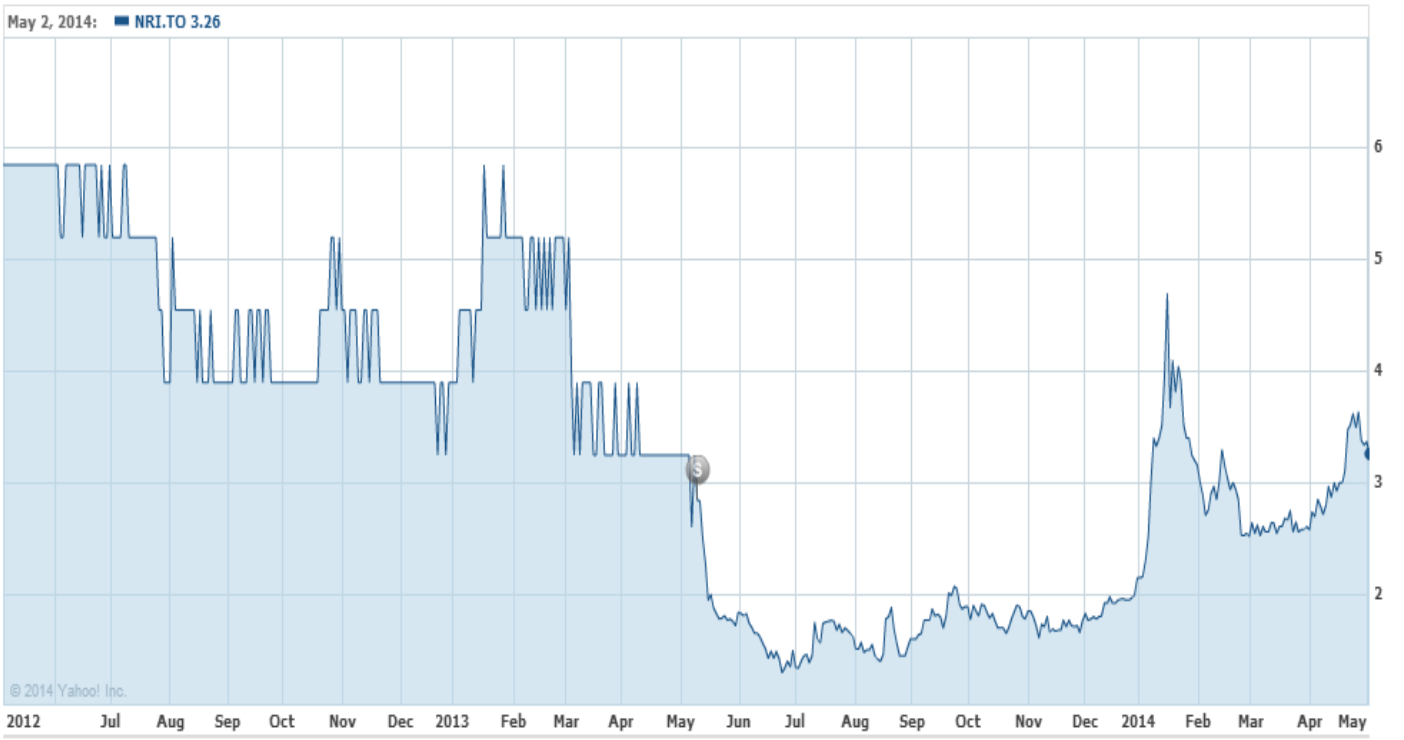
Nuvo Research, Inc.
Income Statement

Nuvo Research, Inc.	2013 A	Q1 A	Q2 E	Q3 E	Q4 E	2014 E	2015 E	2016 E
Revenue from Product Sales	**$4.4**	**$1.2**	**$1.5**	**$1.5**	**$1.5**	**$5.7**	**$5.0**	**$3.0**
YOY Growth	*-50.4%*	-	-	-	-	*27.6%*	*-11.6%*	*-40.0%*
Royalties	**$6.1**	**$1.4**	**$1.4**	**$1.5**	**$1.5**	**$5.8**	**$7.5**	**$13.0**
YOY Growth	*-26.4%*	-	-	-	-	*-4.9%*	*29.4%*	*73.3%*
Licensing Fees	**$7.6**	**$0.1**	**$0.3**	**$0.3**	**$0.3**	**$1.0**	**$1.0**	**$1.5**
YOY Growth	*4.9%*	-	-	-	-	*-87.4%*	*4.5%*	*50.0%*
Research and Contracts	**$0.3**	**$0.1**	**$0.1**	**$0.1**	**$0.1**	**$0.4**	**$0.5**	**$0.5**
YOY Growth	*52.8%*	-	-	-	-	*64.3%*	*11.9%*	*0.0%*
Total Revenues	**$18.4**	**$2.8**	**$3.3**	**$3.4**	**$3.4**	**$12.9**	**$14.0**	**$18.0**
YOY Growth	*-25.3%*	-	-	-	-	*-30.2%*	*8.9%*	*28.6%*
CoGS	$4.8	$1.2	$1.2	$1.3	$1.5	$5.2	$4.0	$2.0
Gross Income	$13.6	$1.5	$2.1	$2.1	$1.9	$7.6	$10.0	$16.0
Product Gross Margin	*74.1%*	*56.1%*	*63.6%*	*61.8%*	*55.9%*	*59.5%*	*71.4%*	*88.9%*
R&D	$7.0	$1.9	$1.9	$2.0	$2.0	$7.8	$9.0	$11.0
% R&D	*38.2%*	*68.4%*	*57.6%*	*58.8%*	*58.8%*	*60.6%*	*64.3%*	*61.1%*
SG&A	$10.1	$2.4	$2.4	$2.5	$2.6	$9.9	$11.0	$12.0
% SG&A	*55.0%*	*86.1%*	*72.7%*	*73.5%*	*76.5%*	*76.8%*	*78.6%*	*66.7%*
Other expenses	$0.6	$0.0	$0.3	$0.5	$0.5	$1.3	$0.5	$0.5
% Payment	*3.1%*	*0.4%*	*9.1%*	*14.7%*	*14.7%*	*10.2%*	*3.6%*	*2.8%*
Operating Income	($4.1)	($2.7)	($2.5)	($2.9)	($3.2)	($11.3)	($10.5)	($7.5)
Operating Margin	*-22.1%*	*-98.7%*	*-75.8%*	*-85.3%*	*-94.1%*	*-88.1%*	*-75.0%*	*-41.7%*
Total Other Income	($6.2)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($10.3)	($2.7)	($2.5)	($2.9)	($3.2)	($11.3)	($10.5)	($7.5)
Taxes & Other	$0.1	$0.0	$0.1	$0.1	$0.1	$0.1	$0.1	$0.1
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Divs. Of Preferred	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Net Income	($10.4)	($2.7)	($2.6)	($3.0)	($3.3)	($11.4)	($10.6)	($7.6)
Net Margin	*-56.4%*	*-99.5%*	*-78.8%*	*-88.2%*	*-97.1%*	*-88.8%*	*-75.7%*	*-42.2%*
Gain/Loss on trans. of foreign ops	$0.0	$0.1	$0.1	$0.1	$0.1	$0.4	$0.2	$0.2
Comprehensive Income	($10.4)	($2.7)	($2.5)	($2.9)	($3.2)	($11.0)	($10.4)	($7.4)
Reported EPS	**($1.18)**	**($0.31)**	**($0.25)**	**($0.29)**	**($0.32)**	**($1.15)**	**($1.01)**	**($0.69)**
YOY Growth	*-23.6%*	-	-	-	-	*-2.2%*	*-12.4%*	*-31.6%*
Shares Outstanding	8.8	8.9	10.2	10.3	10.3	9.9	10.5	11.0

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

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HISTORICAL ZACKS RECOMMENDATIONS



Initiations of Coverage – May 5, 2014 @ $3.26 per share

Chart By: Yahoo!, Inc.

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Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

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