

Avenue Therapeutics, Inc.

(ATXI - NASDAQ)

No Pain? We See a Gain; Developing Tramadol

Based on our DCF model and a 15% discount rate, ATXI is valued at approximately \$19.00 per share. Our model applies a 50% probability of eventual IV tramadol sales for operative pain based on historical Phase 3 success ratios. Our valuation includes geographic contributions from the US only.

Current Price (4/6/2018) **\$4.75**
Valuation **\$19.00**

INITIATION

Avenue Therapeutics is developing IV tramadol for use in a hospital setting where moderate to moderately severe pain relief is required. The candidate is currently in a Ph 3 orthopedic surgery study which is expected to read out in 2Q:18.

A Ph 3 soft tissue surgery study is planned for 3Q:18 concurrent with the ongoing safety study, both of which should provide data by 2Q:19. The company's trials are centered on bunionectomy, abdominoplasty and safety which are to be included in an NDA submission targeted for 2019.

IV tramadol may fill a void in the pain continuum with multi-modal benefits potentially reducing the need for schedule II opioids and addressing the associated side effects of both opioids and NSAIDs. There are ~50 million surgeries and 300 million pain prescriptions written providing a large end market with an unmet need.

ATXI holds sufficient capital to complete the currently active studies. Based on our assessment of market penetration, we initiate with a target price of \$19.00 per share.

SUMMARY DATA

52-Week High	8.58
52-Week Low	3.40
One-Year Return (%)	N/A
Beta	N/A
Average Daily Volume (sh)	25,334

Shares Outstanding (mil)	10.3
Market Capitalization (\$mil)	48.8
Short Interest Ratio (days)	0.11
Institutional Ownership (%)	1.4
Insider Ownership (%)	37.3

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 2017 Estimate	N/A
P/E using 2018 Estimate	N/A

Zacks Rank	N/A
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Risk Level	Above Average
Type of Stock	Small-Growth
Industry	Med-Biomed/Gene

ZACKS ESTIMATES

Revenue

(In millions of US\$)

	Q1	Q2	Q3	Q4	Year
	(Mar)	(Jun)	(Sep)	(Dec)	(Dec)
2017	\$0.0 A				
2018	\$0.0 E				
2019					\$0.0 E
2020					\$0.0 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
	(Mar)	(Jun)	(Sep)	(Dec)	(Dec)
2017	-\$0.07 A	-\$0.70 A	-\$0.30 A	-\$0.50 A	-\$1.85 A
2018	-\$0.68 E	-\$0.67 E	-\$0.69 E	-\$0.70 E	-\$2.74 E
2019					-\$2.72 E
2020					-\$1.13 E

INITIATING COVERAGE

Avenue Therapeutics (NASDAQ: ATXI) is developing IV tramadol for postoperative pain. The drug has been approved by the FDA since 1995; however, only in oral form. Avenue has licensed a patented administration of IV tramadol that is able to limit side effects and provide a solution for moderate to severe pain which avoids many of the risks of opioids and non-steroidal anti-inflammatory drugs (NSAIDs). The drug also allows for transition to step down therapy with oral tramadol, which mirrors the pharmacokinetic, side effect profile and pain control of the IV form.

Tramadol is an attractive alternative to Schedule II opioids and NSAIDs as it is naturally a multi-modal approach to pain management. The drug acts as both an agonist upon the μ -receptors and inhibits both serotonin and noradrenaline reuptake which provides a synergistic benefit in pain control. There exists a gap in the postsurgical setting where moderately severe pain control is required and there are limitations and contraindications with other analgesics making effective pain control difficult. Tramadol may avoid the bleeding risk, gastrointestinal side effects, respiratory depression and risk of dependence that other options carry in the post-operative pain management setting. With the completion of successful clinical trials, we see a solution for the unmet need in this space and a drug that can treat moderate to moderately severe pain that avoids some of the negatives often observed with traditional opioids and NSAIDs.

Avenue currently holds only one development product in its portfolio, IV tramadol, which is currently undergoing two Phase III trials. One is a bunionectomy study which is examining the sum of pain intensity differences over 48 hours in this orthopedic model. A safety study is also underway. Following the anticipated read out of the bunionectomy study in 2Q:18, Avenue will begin a second Phase III study in a soft tissue model that is scheduled to start in 3Q:18. Based on company guidance, both the safety study and the soft tissue study are expected to read out by mid-2019 followed by the submission of an NDA to the FDA using the 505(b)(2) route of approval.

As a result of a 2Q:17 initial public offering, Avenue raised gross cash proceeds of \$38 million. On December 31, 2017, Avenue held approximately \$21.8 million in cash and short term investments on its balance sheet. We expect the company to burn an average of \$5 million per quarter in clinical trial and operational costs as it pursues regulatory approval of IV tramadol. The company currently holds sufficient cash to complete the two in-progress Phase III trials for bunionectomy and safety; however, Avenue will need to raise additional capital prior to the launch of the Phase III soft tissue study, which we expect to take place following the bunionectomy read out.

The unmet need in the postoperative pain space creates an opening for IV tramadol which addresses many of the risks, limitations and contraindications for other entries in the pain control continuum. The favorable characteristics of IV tramadol including its relatively low potential for abuse and multi-modal mechanism of action are supportive of material penetration into this 300 million prescription per year market. We initiate on the shares of Avenue Therapeutics with a target price of \$19.00.

INVESTMENT THESIS

Pain control in surgery runs along a continuum where mild to severe pain treatment is needed. Currently there is a gap in the acute care space between moderate and severe pain control where the risk of conventional opioids is too high and IV acetaminophen provides insufficient analgesia. IV tramadol can successfully fill this space and address patients who may have susceptibility to adverse events or contraindications that prevent the use of some analgesics.

The current movement in pain control seeks to limit the use of opioids and employ multi-modal approaches that maximize efficacy and minimize side effects. The concept hypothesizes that agents with different mechanisms of analgesia may have synergistic effects on addressing acute pain when used together. Tramadol is an example of a drug that has a dual mechanism of action that gives it opioid-like efficacy with less abuse potential. In addition to being a weak μ -receptor agonist, the drug is able to block pain signals at both the spinal column and the brain by inhibiting the norepinephrine and serotonin re-uptake pathway.

Tramadol is well-understood and widely used globally. It was initially approved in 1995 and now accounts for 20% of all US opioid prescriptions and 10% of post-operative IV analgesic use in the EU.

IV tramadol was licensed from Revogenex Ireland for development in the United States with patent protection until 2036 for which Avenue will pay milestone payments and royalties. The desire to reduce the use of opioids, their related side effects and addiction potential as well as the material population for which NSAIDs are insufficient or inappropriate creates an opening for IV tramadol. There are approximately 50 million surgeries that fall along the continuum of post-surgical pain care and 300 million prescriptions for injectable analgesics written annually.

Key reasons to own ATXI shares:

- **Phase III IV Tramadol Asset with NDA Expected in 2019**
 - **IV Tramadol Fills Gap in Pain Treatment Continuum**
 - **Avoids IV Opioid and IV NSAID Contraindications**
 - **Relatively Low Potential for Abuse**
 - **Multi-modal Action**
- **Completion of Registrational Studies Anticipated in 2019**
- **505(b)(2) Route of Approval**
 - **Historically Shorter than 505(b)(1) Pathway**
 - **Historically Higher Rates of Approval vs. 505(b)(1) Pathway**
- **Pursuing Hospital Market of 300 Million Units**
- **Sufficient Cash to Complete Currently Active Trials**

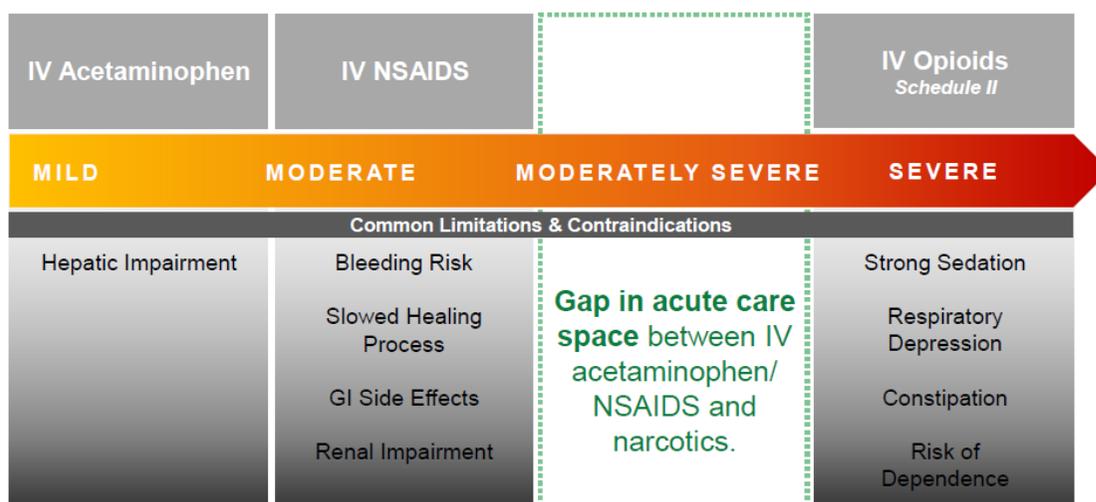
In the following sections we frame the post-operative paradigm of pain control, examining the continuum from mild to severe pain and the gap that exists along this horizon. We also review the risks of the commonly used analgesics used in the post-operative setting and explore the addiction potential with Schedule II opioids. We compare this with IV tramadol's profile and examine the relative addiction risk of the drug compared to Schedule II opioids. IV tramadol has many characteristics that can address shortcomings that exist and we believe the drug can carve out a meaningful market share. Currently used in Europe, the analgesic has proven its worth in large populations. The report also reviews the development of the candidate and the trial design being used. With favorable outcomes expected from the three Phase III trials, we anticipate a successful 2020 launch of the product. Our valuation, derived from our DCF model, is described in detail in the Valuation section. The product of our work generates a target price of \$19.00 per share.

Use of Analgesic in Surgical Setting

Millions of Americans undergo surgery every year in both in-patient and outpatient settings and there is broad use of IV analgesics that range from acetaminophen to NSAIDs and opioids. There are many situations where commonly used analgesics work well, especially for mild to moderate pain in patients without contraindications or predilection towards common side effects. However, there are gaps of unmet need that can be addressed by IV tramadol.

Acetaminophen (Tylenol), NSAIDs and opioids are most commonly used for pain control in the surgical setting. Acetaminophen and NSAIDs are not always sufficient to address moderately severe pain and in many cases it is preferable to avoid opioids due to contraindications and the potential for abuse. The potential for abuse has led many stakeholders in patient care to advocate for limiting the use of opioids when not necessary. While in many circumstances severe pain can only be addressed with Schedule II opioids such as fentanyl, morphine or hydromorphone, in other cases an alternative without the risks of this class is appropriate. Due to side effects or contraindications, it may be preferable to avoid acetaminophen or NSAIDs in specific patient circumstances. These considerations leave a gap in pain management for both patients that are contraindicated for the use of the listed drugs or have pain that falls between moderate and severe. Tramadol may be able to fill this gap in the pain continuum and also avoid common limitations and contraindications.

Exhibit I – Current Post-Operational Pain Management Paradigm



Methods of Pain Control

Non-steroidal anti-inflammatory agents (NSAIDs) are a common approach used to reduce opioid usage and work by inhibiting the enzyme cyclooxygenase, which blocks the production of prostaglandins and limits inflammation. However, there is a risk of bleeding with NSAIDs. The most common NSAID used is ketorolac, which can reduce narcotic consumption when used in combination. Acetaminophen is also widely used, however, in high doses it can be hepatotoxic.

NSAID Side Effects and Contraindications

NSAIDs have specific side effects including increased post-surgery bleeding, peptic ulcer disease, renal impairment, and hepatic damage. The use of NSAIDs may substantially increase the risk of gastrointestinal events. This risk can include peptic ulcer, perforation, obstruction, and bleeding. The kidney can also suffer from adverse events in 1 to 5% of cases.¹ Contraindications for NSAIDs apply to patients with an allergy to aspirin or any NSAID, or who are pregnant or breastfeeding. They also apply to individuals taking blood thinners, or who have coagulation problems, hypertension, liver disease or are older than 75, due to risk of gastrointestinal bleeding and renal failure. Active peptic ulcers and use with bone damage are also contraindications.

¹ http://www.who.int/selection_medicines/committees/expert/21/applications/Grunethal_tramadol.pdf

Opioid Side Effects and Contraindications

There are a number of common side effects from using opioids including sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression. Respiratory depression is of particular concern, as it can result in hypoxia and respiratory arrest. As a result, patients must be monitored for respiration and oxygen saturation when being administered opioids postoperatively. Physical dependence and addiction are clinical concerns that may result in inadequate pain management. Less common side effects include delayed gastric emptying, hyperalgesia, immunologic and hormonal dysfunction, muscle rigidity and myoclonus. Two common groups with elevated risk for opioid use are patients over 65 years of age and obese patients. Older patients may be more at risk as they may be taking other medications and are more likely to have comorbidities. Also, due to lower levels of dopaminergic, serotonergic, cholinergic and GABAergic transmitters, ketamine, benzodiazepines and propofol may produce delirium and/or an increase in efficacy when given together with opioids.² Obese patients have an altered pharmacokinetic profile which can lead to physiologic changes in the response to opioids. Patients with a high body mass index are more susceptible to drug-induced respiratory depression and upper airway obstruction.

Treatment

Treatment of pain and inflammation following surgery is an important component in the healing process to reduce suffering and prevent complications. Multi-modal therapies are recommended due to their synergistic effect and ability to reduce the usage of opioids. Patients without contraindications are frequently prescribed NSAIDs and/or acetaminophen, but there is uncertainty regarding the potential side effects, especially in some types of surgery. Other approaches such as transcutaneous electrical nerve stimulation (TENS) therapy or cognitive-behavioral therapies may be used. Oral medications may be used when they can be taken, but IV administration is preferred due to its rapid response. Patient controlled analgesia is also appropriate in the post-operative setting. As noted elsewhere, there are gaps in treatment for specific levels of pain in patients with adverse effects and/or contraindications.

Pricing

At launch, IV acetaminophen was listing between \$14 and \$15 per vial, but it increased to \$35 per vial following the acquisition by Mallinckrodt (NYSE: MNK), which led to a decrease in market share. Generic NSAIDs and opioids are inexpensive costing usually less than \$6 per dose for IV hydromorphone and ketorolac. At current prices, IV acetaminophen is from \$140 to over \$200 per day at the recommended four to six doses. Generally, post-operative analgesia is a small proportion of total procedure costs.

Sales of analgesics delivered via parenteral routes (IV, subcutaneous, and intramuscular injections) for the management of acute pain totaled approximately \$965 million in the United States in 2013 and injectable analgesics sold near \$1 billion in 2017 according to IMS Health.³

Competing Products in Development

Cara Therapeutics is developing a κ -opioid agonist called CR845, which is in an IV formulation and in Phase 3 development. It has low selectivity for the μ -receptor and the company believes that they can avoid many of the related adverse events such as respiratory depression, nausea, sedation and euphoria/addiction.

Trevena is developing a μ -receptor agonist called Olinvo for the treatment of moderate to severe acute pain when an IV formulation is needed. The drug received breakthrough therapy status from the FDA and has submitted an NDA, which has been accepted by the regulator.

² Freye, E. Use of opioids in the elderly -- pharmacokinetic and pharmacodynamic considerations. *Anesthesiol Intensivmed Notfallmed Schmerzther.* 2004 Sep;39(9):527-37.

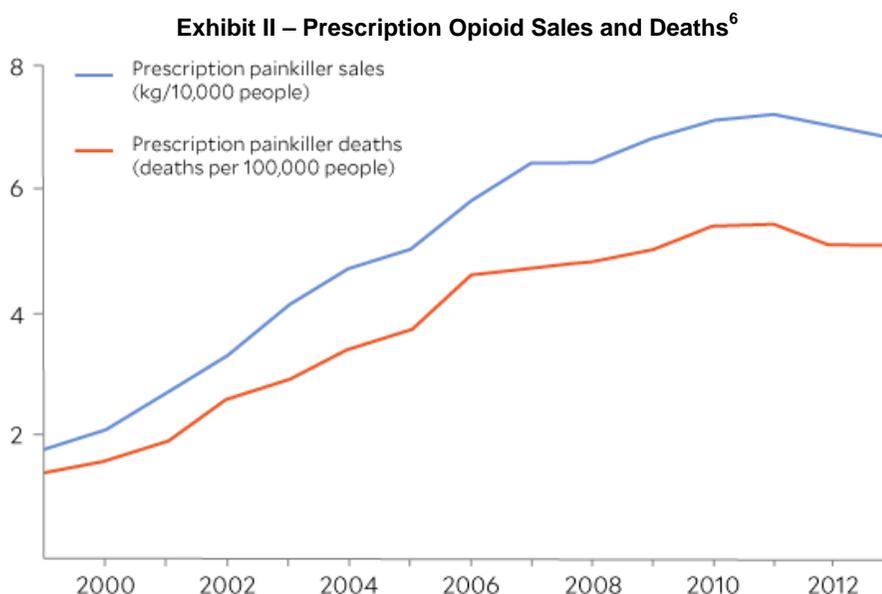
³ Sourced from ATXI 2017 10-K.

Multi-modal Opioid Sparing

To address both the treatment of pain and the reduction in the use of opioids, sparing techniques are used. These approaches seek to address multiple pain pathways including the μ -opioid receptor, κ -opioid receptor, inhibition of COX-1 and COX-2, inhibition of serotonin-norepinephrine and others. This is many times achieved through the combination of NSAIDs and opioids, regional anesthesia/analgesia, and multimodal analgesia, which may decrease the need for powerful opioids.⁴ Tramadol is an attractive option in a multi-modal approach as it has a dual mechanism of action which binds to both μ -opioid receptors and inhibits the neuronal reuptake of norepinephrine and serotonin.

Opioid Crisis

The opioid crisis is one of the most devastating problems facing the United States. Based on data from the CDC, 66% of drug overdose deaths involve an opioid and about 115 Americans die every day from an opioid overdose. Some trace the excesses in opioid abuse to the 1990s change in emphasis on treating pain. During this decade, the leading thought was that pain represented the “Fifth Vital Sign,”⁵ and it was not treated sufficiently. Studies also emerged that downplayed addiction and enumerated the benefits of pain treatment with opioids. In later years, the increase in painkiller prescriptions was closely tied to prescription painkiller deaths.



Certain populations were more prone to abuse than others. Factors that led to a higher than average rate of extended use were tobacco and alcohol use, substance abuse, depression, and other non-surgical related pain suggesting that these groups would particularly benefit from a less addictive type of pain control.

The use of opioids for pain control have come under fire in recent years due to the increasing incidence of addiction, abuse and overdose of the drug class. One of the factors contributing to the opioid epidemic is patients that initially are prescribed opioids by their physician. One study found that many of the overdoses occur in patients using the class for temporary pain relief.⁷

A study that examined post-surgical opioid use found that the longer an individual was prescribed opioids after surgery, the more likely it was that they would become persistent users of the drug.⁸ The study also found that about 6% of those who underwent surgery and were prescribed opioids continued to use them 90 days after surgery.

⁴ Garimella, V.; Cellini, C.; Postoperative Pain Control. Clin Colon Rectal Surg. 2013 Sep; 26(3): 191–196. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747287/>

⁵ The American Pain Society Quality of Care Committee provided guidelines in a 1995 JAMA article identifying pain as a “fifth vital sign” and highlighted their perception of the undertreatment of the condition.

⁶ National Vital Statistics System, Drug Enforcement Administration.

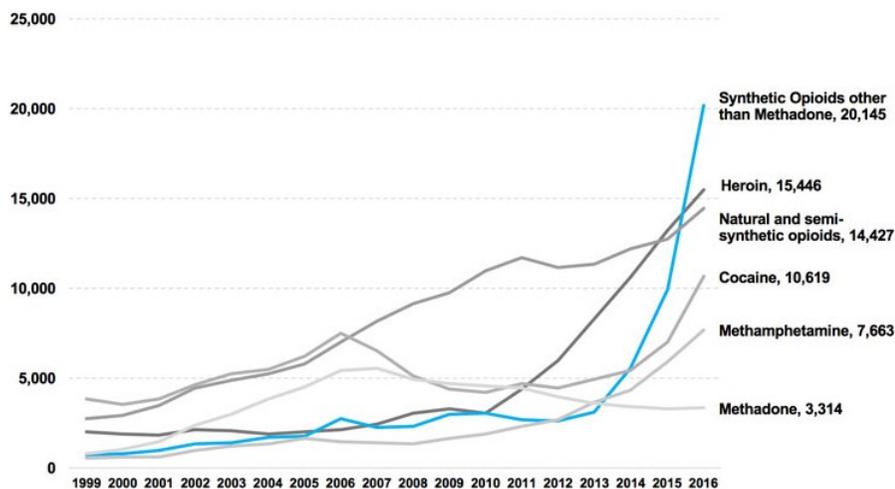
⁷ Brat, Gabriel; et al.; Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. December 17, 2017. BMJ 2018;360:j5790 <http://dx.doi.org/10.1136/bmj.j5790>

⁸ Brummett, Chad, MD; et al.; New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surgery. 2017;152(6)

The drive in recent years in pain control is to move away from the use of addiction-prone opioids and more toward more benign analgesics. This shift has increased the emphasis on multi-modal approaches to pain relief and opioid sparing techniques. Tramadol fits well into this model, as it has a very low likelihood of abuse and avoids many of the side effects common with Schedule II narcotics.

In recent years, overdose deaths have increased substantially, especially for synthetic opioids, including fentanyl, which have become the drug of choice for many abusers. One of the most shocking events in the last few years was the death of musician Prince from fentanyl, highlighting the importance of moving away from potent opioids in the hospital setting.

Exhibit III – Drugs Involved in U.S. Overdose Deaths⁹



As a result of the crisis, there is a strong push to limit the use of addictive opioids for pain control and find alternatives that can address the pain with more acceptable risks. In many cases, hospitals have tried to substitute other drugs such as Tylenol, celecoxib and NSAIDs. Tramadol could also be one of these alternatives given its capability to address moderately severe pain and because it is also considered a safe, low-level opiate medication with the ability to address moderately severe pain.

Addiction and the Opioids that Cause It

Opioids can cause both physical and psychological addiction. Physical dependence related to how a substance can affect the body and the brain in contrast to emotional effects. This type of addiction is generally followed by withdrawal symptoms when the user stops taking the drug. The other type of addiction is psychological and related to an emotional attachment one has to a substance. Many activities such as eating, pleasurable experiences or drugs can create this behavior and reward system. For drugs such as opioids, both of these addictive qualities may be present, highlighting the importance of avoiding them.

The American Academy of Pain estimates that over a quarter of Americans suffer from chronic pain from a wide variety of sources. The National Health Interview Survey finds that over 11% of American adults have suffered some type of pain every day over the past three months. One segment of this pain population are those that have had surgery which is about 48 million persons in 2010, according to the National Health Statistics Report.¹⁰

One of the ways this group is first introduced to potent opioids is following surgery.¹¹ About six percent of patients prescribed opioids following surgery show some level of misuse or abuse¹² and experts attribute at least some of the epidemic to overprescribing.¹³ Other data show that 75% of abusers identified a prescription opioid as their first opioid drug.¹⁴ This has led to changes in behaviors by hospitals including surgeons at the University of Michigan who are encouraging the use of lower-strength, non-addictive painkillers first.¹⁵ Tramadol, again, appears to address the existing concerns and provide a solution to the addiction issue.

⁹ CDC WONDER. <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>

¹⁰ <https://www.cdc.gov/nchs/data/nhsr/nhsr102.pdf>

¹¹ <https://www.npr.org/sections/health-shots/2017/11/26/558792020/should-hospitals-be-punished-for-post-surgical-patients-opioid-addiction>

¹² <https://health.usnews.com/health-care/articles/2018-01-30/how-to-avoid-opioid-addiction-after-surgery>

¹³ <https://www.healthline.com/health-news/doctors-urged-to-reduce-opioids-after-surgery#1>

¹⁴ <https://www.drugabuse.gov/publications/research-reports/relationship-between-prescription-drug-heroin-abuse/prescription-opioid-use-risk-factor-heroin-use>

¹⁵ <https://www.npr.org/sections/health-shots/2017/12/06/568806212/surgeons-try-prescribing-fewer-opioids-to-lower-addiction-risk>

Schedule I to V Controlled Substances

Controlled substances are divided into five categories depending on a drug's safety, medical use and abuse or dependency potential and the DEA and FDA interpretation of these factors. The key element determining the scheduling is the abuse rate, with the likelihood of abuse declining as a substance moves from I to V. Schedule I substances have a high potential for abuse, and have no accepted medical use. Prescriptions are not allowed for this group. Schedule II drugs also have a high potential for abuse but are allowed for medical treatment. Use or abuse of these drugs can lead to severe psychological or physical dependence. Schedule III drugs have less potential for abuse than those classified in I or II, but may still be abused. Schedule IV constituents have a low potential for abuse relative to Schedule III and have an accepted medical use. Abuse may lead to limited physical dependence on the substance. Schedule V have the lowest potential for abuse and there is a limited amount of physical and psychological dependence as a result of using the drug.

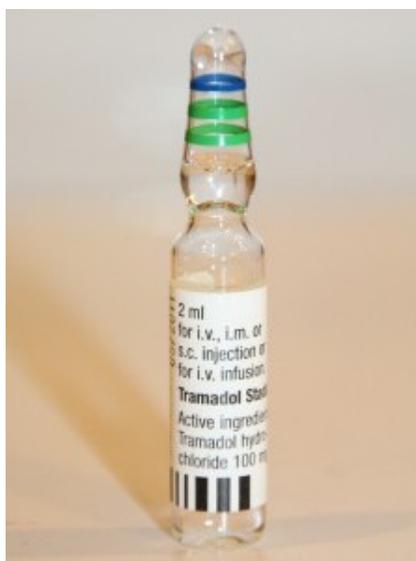
Exhibit IV – Controlled Substance Scheduling

Schedule	Potential For Abuse	Med Use?	Examples
I	Very High	No	Heroin, LSD, MDMA
II	Very High	Yes	Fentanyl, Hydrocodone, Morphine
III	Lower than II	Yes	Buprenorphine, Ketamine
IV	Lower than III	Yes	Tramadol, Benzodiazepine, Barbituates
V	Low	Yes	Pyrovalerone, diphenoxylate

Tramadol

Tramadol was developed by the German pharmaceutical company Grunenthal during the 1960s and was approved and brought to market in 1977 as Tramal. It was not approved in the United States until 1995 under the trade name Ultram and was marketed as an oral capsule/tablet for moderate to moderately severe pain in adults. In 2014, the Department of Justice placed tramadol into Schedule IV for controlled substances.

Exhibit V – Tramadol Ampule¹⁶



Tramadol is used to relieve moderate to moderately severe pain and can be used in conjunction with acetaminophen and ibuprofen. While it is a Schedule IV substance, it can still cause withdrawal if used for a long time. Side effects are mild at the anticipated 50 mg dose but can include nausea, vomiting, constipation, lightheadedness, dizziness, drowsiness and headache.

The pharmacodynamics and pharmacokinetics of tramadol are well understood, illustrating that the analgesic is particularly useful in step down therapy from the IV version to the oral version following discharge after surgery. IV

¹⁶ Each unit of IV Tramadol consists of glass ampoules of 50 mg of tramadol HCl and sodium acetate as buffering agent in 1 mL of water for injection or 100 mg of tramadol HCl and sodium acetate as buffering agent in 2 mL of water for injection. The final drug product is stable at room temperature.

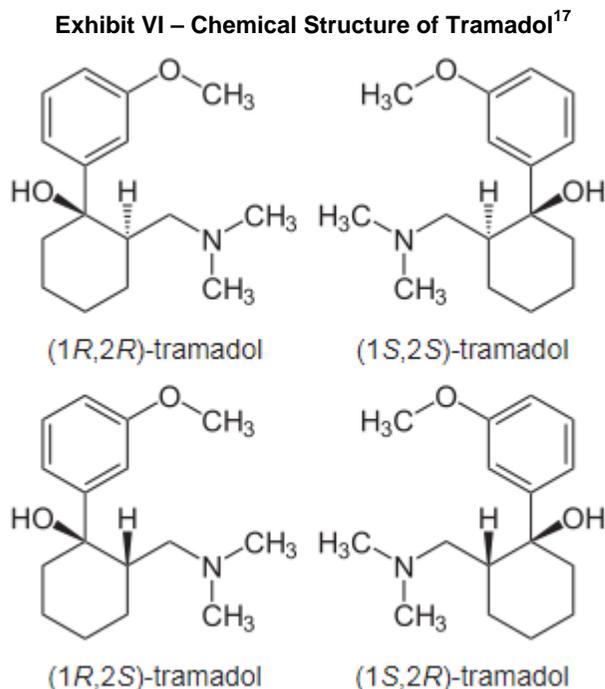
and oral tramadol have a similar C_{max} and AUC. This indicates a smooth transition from the hospital to discharge where the patient can rely on a pain therapy that addresses the same side effects and contraindications that supported the drug's use in the hospital. Switching medications between surgery and discharge can result in unexpected metabolite effects resulting in unexpected safety signals, further supporting consistent use of the same analgesic in both settings.

According to Symphony Health Solutions, approximately 40 million scripts for tramadol and tramadol-containing drugs have been prescribed annually in the United States since 2012.

Mechanism of Action

Tramadol is a non-selective pure agonist for μ , δ , and κ opioid receptors with a higher affinity for the μ receptor. The drug also inhibits neuronal reuptake of noradrenaline and enhances serotonin release. It was originally approved in oral form and later approved in Europe as solution for injection or infusion.

The drug has a low affinity for opioid receptors compared to other opioids and it is the M1 metabolite of tramadol, O-desmethytramadol that confers the analgesic effect via the μ -receptor. The metabolite has a higher affinity for the μ -receptor than tramadol itself and is about 1/30th as potent as morphine. Tramadol's chemical name is 2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol and it is a racemic mixture of two enantiomers, with each showing a different affinity for a specific receptor. The (+)-isomer is a μ -receptor agonist and inhibits serotonin reuptake, while the (-)-isomer inhibits noradrenaline reuptake. The impact of these two enantiomers is synergistic and complementary to the analgesic effect of the drug.



As compared to widely used Schedule IV opioid analgesics, tramadol has a dramatically lower affinity for opioid receptors, reducing the potential for abuse. Tramadol's affinity for μ -receptors is 1/6000th than that of morphine. Also relative to morphine, tramadol is approximately 10% as potent via the parenteral route¹⁸ as the liver does not provide the same degree of first pass metabolism as oral delivery, thereby reducing the concentration of M1 metabolite. The pain reducing ability of tramadol emerges from the multi-modal action of a μ -receptor agonist and the inhibition of noradrenaline and serotonin.¹⁹ The relatively low affinity for μ -receptors is the rationale for the drug to be classified as a Schedule IV opioid rather than the more addictive Schedule II opioids commonly used such as hydromorphone or fentanyl.

¹⁷ Wikipedia contributors. (2018, March 14). Tramadol. In Wikipedia, The Free Encyclopedia. Retrieved 13:42, March 16, 2018, from <https://en.wikipedia.org/w/index.php?title=Tramadol&oldid=830421179>

¹⁸ http://www.who.int/selection_medicines/committees/expert/21/applications/Grunethal_tramadol.pdf

¹⁹ Dayer, P. Pharmacology of Tramadol. *Drugs*. 1997;53 Suppl 2:18-24. <https://www.ncbi.nlm.nih.gov/pubmed/9190321>

In a 2006 article, Edgar Adams conducted a study comparing the relative abuse risk of NSAIDs, tramadol and hydrocodone.²⁰ Subjects were scored for abuse twelve months after treatment and a score of 2.5% was assigned to NSAIDs, 2.7% for tramadol and 4.9% for hydrocodone, illustrating the relatively low risk of abuse. The study concluded that the prevalence of abuse or dependence was equivalent for NSAIDs and tramadol, and significantly less than the rate for hydrocodone. Postmarketing studies identified pharmacodynamic and pharmacokinetic properties of tramadol that make it highly unlikely use of the drug will lead to dependence. The study found that in the first 18 months after the drug's introduction, there were 2 cases of abuse in 100,000 patients. This declined in subsequent periods, and was less than 1 case per 100,000 in the second 18-month period examined. Abuse of tramadol was found to occur in populations that already had a history of drug abuse.²¹ Other research estimated that the incidence rate for tramadol abuse and addiction was 0.69% per year.²²

The drug is an effective analgesic as shown in studies conducted. A review by Krusz measured an average reduction in pain severity from 7.5 to 2.8 in a headache model employing the commonly used visual analog scale (VAS). Side effects were minimal and included transient drowsiness and nausea.²³

Tramadol has pharmacodynamic and pharmacokinetic properties that limit the risk of dependence. Various controlled studies and postmarketing surveillance studies have been conducted, which reported low levels of tolerance or instances of tramadol abuse. This work has shown tramadol to be largely effective and well tolerated, and of value for treating a variety of pain conditions.

Step-down therapy:

Importantly, there is a step-down therapy available for IV tramadol, which allows the same drug to be used in parenteral and oral form. Patients are transitioned to oral tramadol when they are discharged from the hospital or when they can tolerate a pill. This allows for the same pain control benefits and same adverse event and contraindication profile to be maintained. Avenue's IV tramadol dosing regimen provides a similar PK profile to that of oral tramadol at steady state to ensure a smooth step-down process.

Adverse Events and Contraindications

Respiratory depression is a risk with all opioids, however, tramadol has a lower likelihood of respiratory depression compared to pure μ -receptor opioids. The drug can also cause seizure, but not at a higher rate than what is observed in other pain medications. Seizure was mainly observed at high doses. Tramadol should not be used with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase (MAO) inhibitors,²⁴ tricyclic antidepressants and mirtazapine, as they may result in serotonin toxicity. Mixed opioid agonists/antagonists such as pentazocine, nalbuphine, butorphanol and naltrexone may negatively interact with tramadol.

Benefits Compared to Current Treatment Paradigm

IV tramadol has a number of benefits for its target segment of the pain continuum. There are currently three broadly used classes of pain medications available. On the low end of the spectrum is IV acetaminophen which is appropriate for mild pain, but may have issues related to hepatic impairment. Moving to moderate pain, IV NSAIDs are appropriate, however, they are associated with bleeding risk, slowed healing, gastrointestinal issues and renal impairment. For severe pain, Schedule II intravenous opioids are used, but have a host of risks tied to them. Addiction potential, respiratory depression and constipation are some of them and the drug may put the patient in a state of strong sedation which is not appropriate for some surgeries. For patients that are contraindicated for IV NSAIDs and IV opioids and who suffer from moderately severe pain, IV tramadol may be the appropriate option.

²⁰ Adams Edgar H, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll S. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. *J Pain Symptom Management* 2006; 31(5): 465-76.

²¹ Cicero, TJ; et al. A postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. *Drug Alcohol Depend.* 1999 Nov 1;57(1):7-22.

http://cicero.wustl.edu/skip/publications/key_pubs/18%20A%20postmarketing%20surveillance%20program%20to%20monitor%20Ultram.pdf

²² Knisely JS, Campbell ED, Dawson KS, Schnoll SH. Tramadol post-marketing surveillance in health care professionals. *Drug Alcohol Depend* 2002; 68(1):15-22.

²³ Krusz, J. IV tramadol: very efficacious treatment for pain and headache in the outpatient clinic. April 2013 Volume 14, Issue 4, Supplement, Page S71. [http://www.jpain.org/article/S1526-5900\(13\)00659-7/fulltext](http://www.jpain.org/article/S1526-5900(13)00659-7/fulltext)

²⁴ Such as isocarboxazid, linezolid, methylene blue, moclobemide, phenelzine, procarbazine, rasagiline, safinamide, selegiline, and tranylcypromine. These should not be taken for two weeks prior to tramadol use.

Exhibit VII – Tramadol in the Pain Management Paradigm

IV Acetaminophen	IV NSAIDS	IV Tramadol Schedule IV	IV Opioids Schedule II
MILD	MODERATE	MODERATELY SEVERE	SEVERE
Common Limitations & Contraindications			
Hepatic Impairment	Bleeding Risk Slowed Healing Process GI Side Effects Renal Impairment	Nausea/Dizziness History of Seizure Concomitant use of Serotonergic Drugs	Strong Sedation Respiratory Depression Constipation Risk of Dependence
IV Tramadol to avoid use of conventional opioid; Step-down therapy to oral Tramadol			

Summary of IV tramadol benefits:

- Convenience in the post-surgical and acute care setting
- Lower addiction and abuse risk compared to traditional opioids
- Faster onset of action as compared to oral tramadol
- Appropriate for patients who cannot take oral medications
- As patient moves from operating room to discharge, they can shift from IV tramadol to the oral form of the same drug
- Effective analgesia
- Does not cause respiratory depression as do conventional narcotics

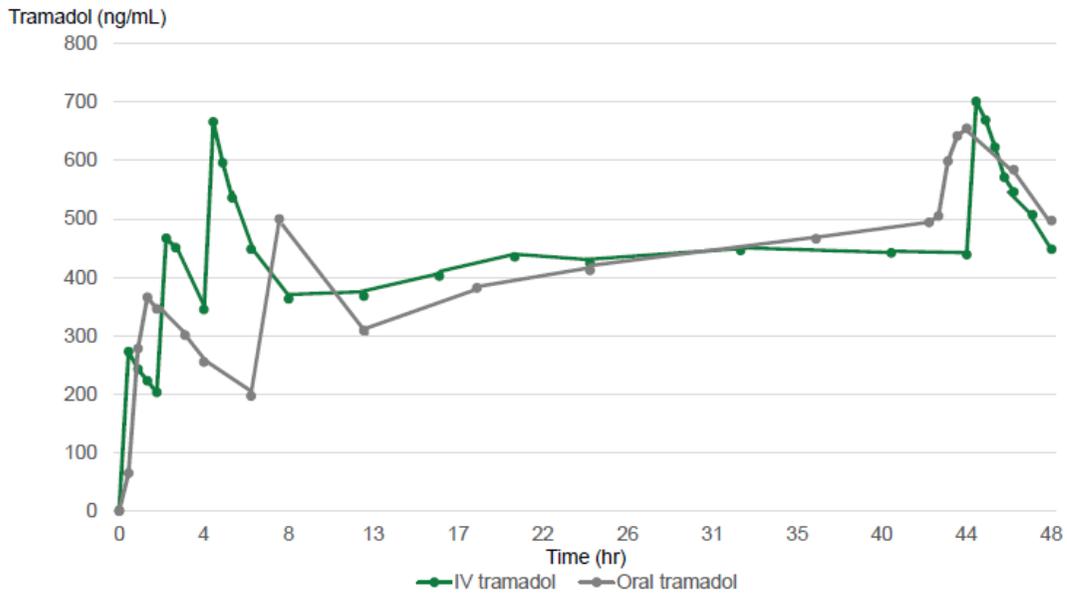
IV Tramadol Clinical History

Preclinical work for IV tramadol was performed by Revogenex, which completed multiple pharmacokinetic and toxicology studies in dogs. Revogenex also conducted Phase I dose proportionality studies in healthy volunteers, which compared IV tramadol with oral tramadol. Additionally, an evaluation of delayed cardiac repolarization following administration of tramadol was assessed in a thorough QT/QTc²⁵ study in healthy volunteers. Given the long history of tramadol and the understanding of the efficacy and dose parameters, Phase II studies were not conducted.

A pharmacokinetic and safety study was performed in 18 healthy volunteers to determine an IV tramadol dose that was equivalent to the oral dose. The study examined the systemic exposure, maximal and minimal levels of drug concentration in the blood and the time to excrete the drug from the body. The study was designed as a three-way crossover, where each of the enrollees acted as their own control. Two IV doses and one oral dose were used in the three arms. The results of the work supported the use of a 50 mg dose for the Phase III segment. Below we highlight the plasma concentration in blood over a two-day period, which shows a close correlation between the oral and IV forms of tramadol.

²⁵ The thorough QT/QTc study examines the impact of an investigational drug on the heart's QT cycle, and assesses it for QT prolongation. In some cases a QT-prolonging drug can lead to drug-induced sudden cardiac death.

Exhibit VIII – Tramadol Concentration vs. Time Curve for IV (50mg) and Oral (100mg)



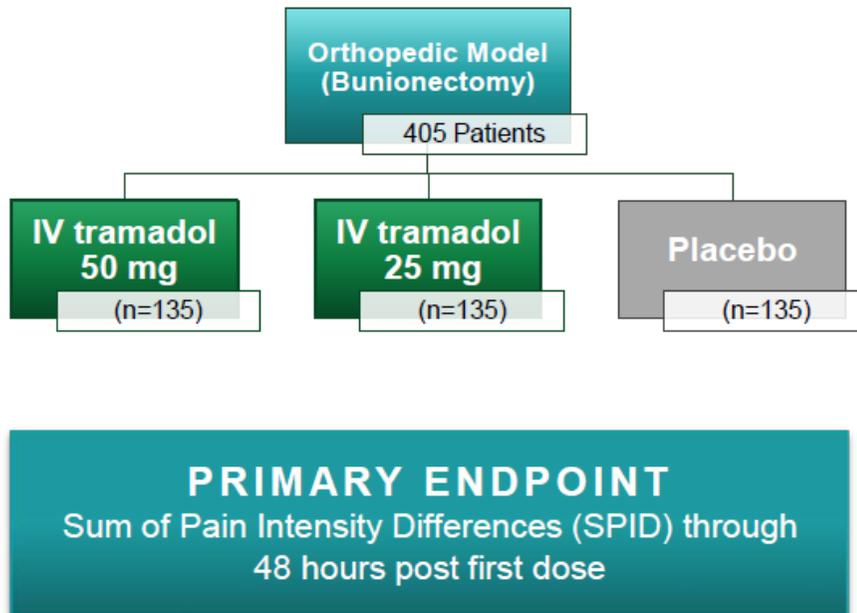
During the end of Avenue’s Phase II meeting with the FDA, the two parties developed the Phase III protocol, which is described below.

Phase III Trial (Bunionectomy)

Avenue’s first Phase III trial, called [Tramadol Versus Placebo in the Management of Postoperative Pain Following Bunionectomy](#) was launched in September 2017 as a Phase III, multicenter, randomized, double blind three arm study. The investigational drug is identified as tramadol infusion (AVE-901) for the management of post-operative pain following bunionectomy. The study is targeting enrollment of 405 patients and is expected to generate a readout in Q2:18. The trial will be broken up into three arms which include 1:1:1 split between IV tramadol at 50 mg, IV tramadol at 25 mg and placebo.

In this protocol, the drug is infused intravenously over 15 minutes at hours 0, 2, 4 and every subsequent four hours. The primary endpoint for the study will be the sum of pain intensity differences (SPID) for the first 48 hours after the initial dose. SPID is a metric that evaluates a treatment response over a defined period of time. It accounts for the level of pain relief and weights it over time providing a single quantitative output.

Exhibit IX – Phase III Orthopedic Model Trial Design



Phase III Safety Study

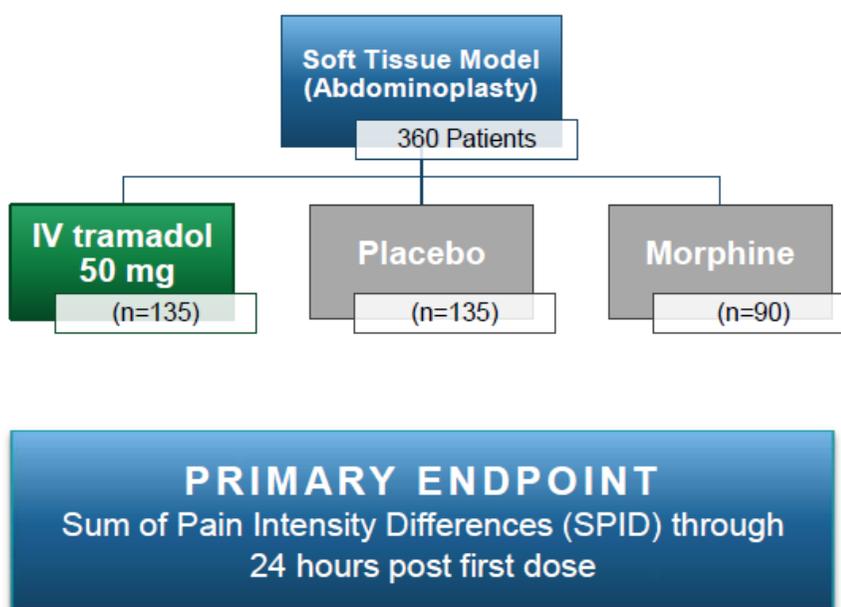
The second Phase III study is titled [Evaluate Safety of Tramadol in the Management of Postoperative Pain Following Surgery](#) and is intended to evaluate the safety of IV Tramadol. It is enrolling 250 patients and was launched in December 2017. The trial will be a multicenter, single-arm open-label study to evaluate the safety of tramadol infusion (AVE-901) in the management of post-operative pain following surgery. Initial estimates are for the trial to be complete by mid-year 2019.

Primary endpoints address safety and examine adverse events up to 21 days following the infusion and infusion site reaction up to 168 hours after last infusion.

Phase III Soft Tissue Model

A third Phase III trial is planned to begin in the third quarter of 2018 which will examine the use of the drug in a soft tissue surgery model following abdominoplasty. It will target 360 patients split into three cohorts including 50 mg of IV tramadol, placebo and morphine in a 3:3:2 ratio. As with the bunionectomy study, the primary endpoint will be the SPID but at a shorter interval of 24 hours following the first dose.

Exhibit X – Phase III Soft Tissue Model Trial Design



Management anticipates that the company can report topline data by mid-2019 for the abdominoplasty study, based on previous trial enrollment rates. This is expected to coincide with the anticipated completion of the safety study.

If the data in the trials are supportive, then the company plans to submit a new drug application to the FDA using the 505(b)(2) pathway. The 505(b)(2) pathway is designed for medicines that are known chemical entities, but are different in a meaningful way, such as dosage or method of administration. This will allow it to rely on safety and efficacy data originated by the sponsor, Janssen Pharmaceuticals. Avenue will rely upon previously published literature and the FDA's findings of safety and effectiveness for its submission.

Chemistry, Manufacturing and Control (CMC)

Avenue uses a contract manufacturing organization (CMO) to manufacture its active pharmaceutical ingredient (API) IV tramadol. The current agreement with the manufacturer has minimum purchase agreement volumes for a five-year period following approval. The agreement with the CMO involves a payment of a fixed fee per unit and a low single digit royalty on sales revenue. The company will also pursue a backup manufacturer but will not begin the search efforts until the Phase III trials are complete.

Intellectual Property

Avenue holds four patents related to the intravenous administration of tramadol which expire from 2032 to 2036. In the United States a novel dosing regimen can be patented, unlike in Europe. The company has licensed the right to develop the patents originated by Revogenex Ireland Ltd who had completed several preclinical pharmacokinetic and toxicology studies. In February 2015, Avenue parent Fortress obtained an exclusive license from Revogenex to develop and commercialize IV tramadol. Below, we identify the relevant patents for IV tramadol:

Exhibit XI – Intravenous Tramadol Patents

Patent #	Title	Filed	Expiry	Serial	Assignee
8,895,622	Intravenous administration of tramadol	12-Apr-12	2032	13/445,526	Revogenex
9,561,195	Intravenous administration of tramadol	21-Nov-14	2032	14/550,279	Revogenex
9,566,253	Intravenous administration of tramadol	15-May-15	2032	14/713,775	Revogenex
9,693,949	Intravenous administration of tramadol	24-May-16	2036	15/163,111	Revogenex

Each of the patents claim a method for administering tramadol using an intravenous dosing regimen. The invention identifies an initial dose of 50 mg at time zero followed by a second dose of 50 mg at two hours after the first dose, and then a subsequent dose of 50 mg after another two hours. Following the third dose, subsequent spacing is at four hour intervals, administering 50 mg of drug until the patient no longer requires treatment. The 50 mg infusion takes place over a 15 minute period and total treatment time is expected to be over a 24 or 48 hour period.

Financial Position

As of December 31, 2017 Avenue Therapeutics held approximately \$21.8 million in cash and cash equivalents and short-term investments on its balance sheet. In 2Q:17, the company raised gross proceeds of \$38.0 million and net proceeds of about \$34 million in an IPO, which we believe is sufficient to fund the Phase III safety trial and the Phase III orthopedic model. We anticipate expenditures of approximately \$7 million per quarter, but also expect a high degree of volatility due to upfront trial costs and timing of trial-related R&D payments. For the fiscal year ending December 31, 2017, Avenue consumed approximately \$16.8 million in cash from operations. Following the IPO, the company holds no debt or notes payable on its balance sheet. We anticipate a capital raise in the first half of 2018 in order to fund the Phase III soft tissue study.

Management has made clear that current cash levels are only sufficient to support the conclusion of the Phase III safety and bunionectomy study. We assume that Avenue will raise an additional \$50 million to fund the abdominoplasty trial for IV tramadol and to maintain sufficient cash to pay upfront amounts that are due to Revogenex. The actual amount of capital raised will be dependent on market conditions and estimated dilution at the time of issuance.

Key Events

- Initiated Phase III Bunionectomy Study – 3Q:17
- Initiated Safety Study – 4Q:17
- Topline Readout from Phase III Bunionectomy Study – 2Q:18
- Initiate Phase III Abdominoplasty Study – 3Q:18
- Topline Readout from Phase III Abdominoplasty Study – 2Q:19
- Complete Safety Study – 2Q:19
- Submit NDA – 4Q:19
- Anticipated PFUFA Date – 4Q:20
- First Sales – FY:21

RISKS

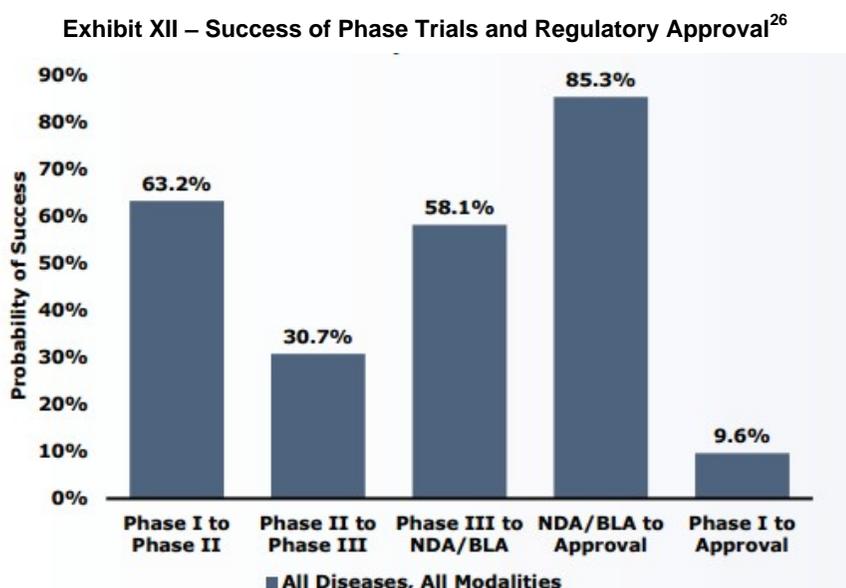
All investments contain an element of risk which reflects the uncertainty of the business and what it will ultimately achieve. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are betting on an emerging technology will have a much higher level.

The biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical powerhouses that have multiple products currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large pharmaceutical companies and smaller biotechnology-focused firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products.

For smaller early-stage companies, investing in drug development is an extended process. The timeframe for conducting pre-clinical research to eventually marketing a new chemical entity can take from 12 to 15 years or even longer given market conditions. And with, on average, only one in one thousand compounds eventually making it to the market, the risks are substantial.

Even if a company has a strong, experienced team that is developing a therapy with a high likelihood of success and a large addressable market, securing funding may pose a substantial risk. Access to financing comes and goes in cycles. During periods of improving confidence, capital may be easy to access; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. If capital is needed to sustain the company and it is not readily available, it may be forced to suspend operations, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route to move forward or force a company to accept onerous terms.

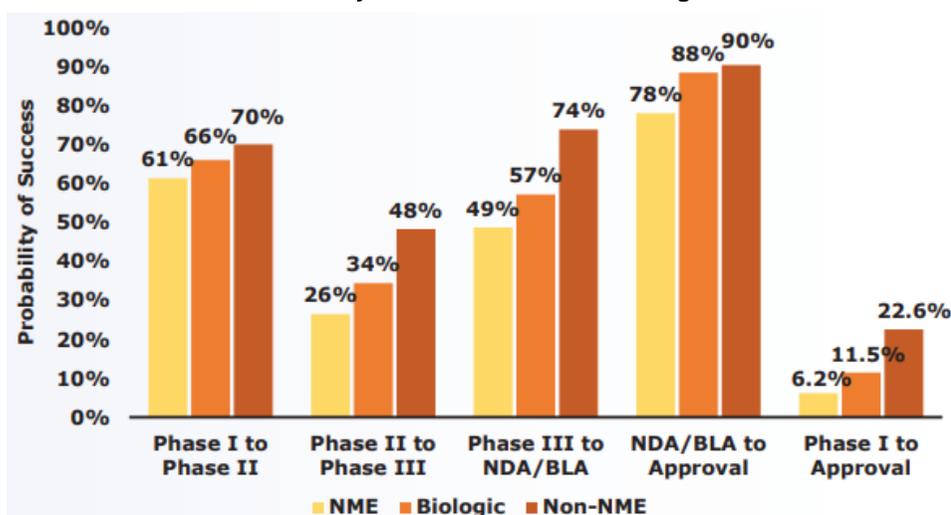
FDA or other governmental regulatory approvals are a material uncertainty to which all drugs must submit before they are legally marketed. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. Isolating companies that have a long history of research success in drug development, with opinion leaders and experts in the field are key elements that can help mitigate this risk. Companies that have had previous success with the FDA or other regulatory agencies also are more attractive than those who may be new to the process. Some accelerated pathways to approval have been put forth such as the Orphan Drug Act; however, changes in sentiment or perceived safety for pharmaceuticals drugs could change the regulatory environment to demand a more thorough process and these pathways may be extended or additional requirements may be put in place.



²⁶ Clinical Development Success Rates 2006-2015. David W. Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

Currently, Avenue Therapeutics is navigating its lead compound through multiple Phase III trials. Historically, Phase III trials have a 50% chance of leading to ultimate FDA approval. Avenue will be using 505(b)(2) pathway for approval, which is a faster and higher probability pathway as compared to a new chemical entity being submitted via an NDA. Based on the data provided in Clinical Development Success Rates, non-NMEs have about a 67% likelihood of approval, a ratio which increases to 90% following the submission of an NDA.

Exhibit XIII – Probability of Success: NME vs. Biologic vs. Non-NME



In recent years, contract research organizations (CROs) have taken on a larger role in the development of drug candidates as the complexity and cost of trials has increased. Finding appropriate populations to participate in clinical trials has become increasingly difficult due to the shift to personalized medicine and orphan indications that address only a small population. This shift has increased the dependence on these specialized CROs for enrollee sourcing, project management and clinical monitoring services which add additional risks and dependence on third parties. Avenue is working with a smaller specialized CRO that focuses on therapeutic areas related to pain.

In addition to CROs, Avenue relies of third party manufacturers for manufacturing test and commercial quantities of IV tramadol. Risks of poor manufacturing processes, quality control issues and product delays may postpone ultimate production of the drug. While Avenue will seek an alternate supplier at some point for IV tramadol, the product is now only manufactured by Z.F. Polpharma S.A. in Europe. The partner may lack the desire or skill to successfully obtain the approvals required to produce cGMP quality product and the partner may have other competing products under its control that receive greater company attention and resources.

Drug price inflation has gained increased attention over the last several years and has contributed materially to the increase in health care costs over the last decades. As new therapies have been approved, drug prices have set new records and increased at a substantial rate. For example, in 1996, new cancer drugs cost roughly \$54,000 for each additional year of life they provided. However, by 2013, this amount increased to over \$200,000. The inflation rate for established drugs has also been very high. In a Forbes article, Novartis' leukemia drug Gleevec was highlighted. This drug cost \$24,000 in 2001 when it was first approved; and 14 years later, in 2015, had risen to a cost of \$90,000. This represents a 10% compound annual growth rate over that period. We also cite the broad response to Mylan's EpiPen price increases which have pressured the company to offer lower priced alternatives and encouraged competitors to accelerate the availability of generics. In the pain space, opioids and NSAIDs are inexpensive and branded tramadol would cost substantially more than these standards to use in the post-operational setting. While the price of the drug would attract attention when examined on a percent increase basis, the total cost of the product for a day of use is not expected to exceed \$100. Furthermore, the use of tramadol may reduce side effects for many patients and the related cost of treatment as well as reduce the likelihood of negative externalities such as opioid abuse and addiction.

While we have discussed a broad variety of risks above, we believe that our forecast parameters, discount rates, success probabilities and valuation metrics address these eventualities and our target price reflects an assumption of these risks faced by all biotechnology companies.

PEERS AND COMPETITORS

There are several other participants in the IV postoperative pain and adjacent spaces including both companies that have products in development and products that are currently generating sales. We include a list of the most relevant peers and competitors below, ranked by market capitalization.

Exhibit XIV – Avenue Therapeutics²⁷

Ticker	Company	Price	MktCap (MM)	EV	Therapeutic Area
JNJ	Johnson & Johnson	\$128.10	\$343,646	\$359,931	Tramadol sponsor via Janssen
RHHBY	Roche Holding	\$28.05	\$192,124	\$199,626	Ketorolac (Toradol)
HRTX	Heron Therapeutics	\$26.75	\$1,889	\$1,720	Bupivacaine
PCRX	Pacira Pharma	\$33.30	\$1,356	\$1,247	Bupivacaine
CARA	Cara Therapeutics	\$11.89	\$389	\$296	IV Difelikefalin (CR845)
REPH	Recro Pharma	\$10.19	\$199	\$188	Meloxicam NSAID
TRVN	Trevena	\$1.63	\$109	\$71	Oliceridine (μ-opioid)
CPIX	Cumberland Pharma	\$6.59	\$103	\$63	Caldolor NSAID
pvt	Purdue Pharma	-	-	-	Dilaudid (hydromorphone)
pvt	Neumentum	-	-	-	Ketorolac & non-opioid analgesics
ATXI	Avenue Therapeutics	\$4.75	\$49	\$27	IV Tramadol

JNJ develops, manufactures and sells a broad portfolio of medical and consumer products globally. Through its subsidiary Janssen, tramadol was sponsored to the FDA and received approval in oral form.

RHHBY is a Swiss-based diagnostics & pharmaceutical company providing medicines in a variety of therapeutic areas. The company currently commercializes Toradol, which is the dominant NSAID used in post-operative pain.

HRTX is a biotechnology company with a portfolio of several products for cancer and post-operative pain. HTX-011 is in clinical development for use as local anesthesia for post-operative pain.

PCRX develops hospital products including liposome injection Exparel, which is used for postsurgical analgesia.

CARA is developing a stable of products in the pruritus and pain categories. Its lead pain indication, CR845 is currently in Ph3 development, indicated for post-operational pain.

REPH develops non-opioid analgesics. Its portfolio of products includes NSAID IV meloxicam being developed via the 505(b)(2) route with May 2018 PDUFA date.

TRVN developing medicines in a variety of indications including moderate to severe acute pain. Lead candidate is IV-based μ opioid receptor Olinvo (oliceidine) for which an NDA has been accepted by the FDA in January 2018.

CPIX has a broad portfolio of development and marketed hospital and gastrointestinal products. Key product Caldolor is an NSAID for management of moderate to severe pain used as an adjunct to opioid analgesics.

Purdue commercializes a portfolio of opioid and pain products. The company markets a lyophilized version of the drug for intravenous use as analgesic used in conjunction with surgical procedures.

Neumentum is a non-opioid analgesic pharmaceutical company with rights to five novel pain products. The company's lead candidates are varied preparations of ketorolac in the later stages of development.

²⁷ Price and market capitalization data is as of April 6, 2018

MANAGEMENT PROFILES

Lucy Lu, President and CEO

Dr. Lu has been Avenue's President and Chief Executive Officer since inception. From February 2012 to June 2017, Dr. Lu was the Executive Vice President and Chief Financial Officer of Fortress Biotech, Inc. Prior to working in the biotech industry, Dr. Lu had 10 years of experience in healthcare-related equity research and investment banking. From February 2007 through January 2012, Dr. Lu was a senior biotechnology equity analyst with Citigroup Investment Research. From 2004 until joining Citigroup, she was with First Albany Capital, serving as Vice President from April 2004 until becoming a Principal of the firm in February 2006. Dr. Lu holds an M.D. degree from the New York University School of Medicine and an M.B.A. from the Leonard N. Stern School of Business at New York University. Dr. Lu obtained a B.A. from the University of Tennessee's College of Arts and Science.

Joseph Vazzano, VP Finance and Corporate Controller

Mr. Vazzano has served as Avenue's Vice President of Finance and Corporate Controller (principal financial and accounting officer) since July 2017. Mr. Vazzano joins Avenue from Intercept Pharmaceuticals, Inc., where he served as Assistant Corporate Controller and oversaw the expansion of the company's finance and accounting department during its transition from development-stage to a fully integrated commercial organization. Prior to Intercept, Mr. Vazzano served as Assistant Controller at Pernix Therapeutics, where he successfully built an accounting and finance team after a corporate restructuring. Earlier in his career, Mr. Vazzano held roles of increasing responsibility in finance and accounting at NPS Pharmaceuticals, a publicly traded biotechnology company acquired by Shire Pharmaceuticals, and was a senior auditor at KPMG, LLP. Mr. Vazzano holds a B.S. in accounting from Lehigh University in Bethlehem, PA, and is a certified public accountant in New Jersey.

Lindsay A. Rosenwald, MD, Executive Chairman

Dr. Rosenwald has served as Executive Chairman of Avenue Therapeutics since inception. He has been Chairman and CEO of Fortress Biotech since December 2013. Since November 2008, Dr. Rosenwald has served as Co-Portfolio Manager and Partner of Opus Point Partners Management, LLC, an asset management firm in the life sciences industry, which he joined in 2009. Prior to that, from 1991 to 2008, he served as the Chairman of Paramount BioCapital, Inc. Over the last 23 years, Dr. Rosenwald has acted as a biotechnology entrepreneur and has been involved in the founding and recapitalization of numerous public and private biotechnology and life sciences companies. Dr. Rosenwald received his B.S. in finance from Pennsylvania State University and his M.D. from Temple University School of Medicine.

Scott A. Reines, MD, PhD, Interim Chief Medical Officer

Dr. Reines has served as Avenue's Interim Chief Medical Officer since January 2016. Dr. Reines has led the clinical development of important new drugs in five different therapeutic areas. As Senior Vice President for CNS, Pain, and Translational Medicine at Johnson & Johnson, he oversaw the development and approval of INVEGA and INVEGA SUSTENNA for schizophrenia, NUCYNTA for moderate to severe pain, REMINYL ER for Alzheimer's disease, RISPERDAL CONSTA for schizophrenia and bipolar disorder, RISPERDAL for treatment of the autism, and TOPAMAX for prevention of migraine and seizures. At J&J he was responsible for all CNS and Pain products, as well as for Clinical Pharmacology and Pharmacogenomics, and was a member of the J&J Pharmaceutical R&D Board of Directors.

Previously, Dr. Reines was Vice President, Clinical Research at Merck, with responsibilities for Psychopharmacology, Neuropharmacology, Gastroenterology, and Ophthalmology. There he led the development of EMEND for prevention of chemotherapy-induced nausea and vomiting, MAXALT for treatment of migraine headache, SINEMET-CR for Parkinson's disease, and TRUSOPT, COSOPT, and TIMOPTIC-XE for prevention of glaucoma.

Currently Dr. Reines consults for biotech, pharmaceutical, and venture firms, is a member of two Scientific Advisory Boards, and Chair of a Data Safety Monitoring Board. He is also a member of two non-profit boards, serving as Vice Chair of the Board of Directors of KidsPeace, a large children's psychiatric healthcare provider, and as a member of the Board of Directors of Heritage Conservancy, which is directed toward land preservation.

Dr. Reines also served for two years as co-chair of the Neuroscience Steering Committee, Foundation for NIH Biomarkers Consortium, and spent five years on the National Drug Abuse Advisory Council. He holds a bachelor's degree in chemistry from Cornell University, a PhD in chemistry/molecular biology from Columbia University, and an MD from Albert Einstein College of Medicine. He is Board Certified in Psychiatry and Neurology.

Financial Results

Avenue Therapeutics filed its 2017 10-K on March 1st 2018 for the year ending December 31, 2017. No revenues were reported in either 2017 or 2016. Net loss for fiscal year 2017 was (\$12.3) million or (\$1.85) per share. This was comprised of operational costs of \$11.4 million, less several below the line items including net interest expense and fair value adjustments. Total research and development expense of \$7.8 million rose 465% over the prior year's amount. Research and development was split between \$1.1 million for licenses and \$6.7 million for core R&D in 2017. Increases in R&D are attributable to the launch and expansion of the bunionectomy study in September 2017 and the initiation of the safety study in December 2017. The increase in R&D licenses was linked to the payment of the stock dividend to Fortress.

General and administrative expenses were \$3.6 million in 2017, rising from \$1.0 million in 2016. The 263% increase came from stock issuance related expenses, which included a common share financing fee paid to Fortress. Other factors contributing to the increase include higher stock compensation expense, personnel costs, market research costs, professional fees and other items.

Cash burn was \$16.8 million in 2017, up substantially from the \$1.6 million in 2016 as management was hired and trials were launched. Cash and equivalents and short-term investments as of December 31, 2017 were \$21.8 million, an increase from year end 2016 levels of \$0.2 million. The increase was attributable to an IPO of 6.3 million shares at \$6.00 per share.

Avenue is a controlled company, with 34% of shares owned by Fortress Biotech (NASDAQ: FBIO). This status affords the controlling shareholder anti-dilutive benefits where Fortress will receive 2.5% of the gross amount of any equity or debt financing. Additionally, an annual dividend of 2.5% of shares outstanding will be paid to Fortress. The parent provides a variety of services under a master services agreement to Avenue which include advice and assistance concerning any and all aspects of Avenue's operations, clinical trials, financial planning and strategic transactions and financings. The agreement also covers the conduct of relations between Avenue and accountants, attorneys, financial advisors and others. In return for these services, Avenue pays a consulting fee of \$500,000 per annum, which may be paid in stock.

VALUATION

The IV formulation of tramadol is prescribed widely throughout the world, but has not yet been approved in the United States. There is a broad patient population that falls into the moderately severe pain segment of the pain continuum. There is also a post-surgical population at a higher risk for adverse events and with contraindications for the current pain management paradigm. This unmet need has been recognized by the pain management community who also acknowledge the potential addiction dangers of Schedule II opioids.

We are initiating coverage of Avenue Therapeutics Inc. with a price target of \$19.00. Avenue's lead clinical stage candidate, IV tramadol, is a proprietary administration of an existing drug approved by the FDA in oral form. Based on the latest data available, in 2014/2015 there were approximately 300 million doses of IV analgesics sold in the United States. About 80% of this total consisted of narcotic analgesics, with the dominant contributors being hydromorphone, morphine, and fentanyl. We believe that a relatively high penetration can be made into the opioid segment given the more favorable profile of IV tramadol compared to these options. Non-narcotic IV analgesics make up approximately 20% of the total with the vast majority made up of ketorolac (77%), and Ofirmev (16%). We believe that IV tramadol can achieve a moderate level of penetration into this group.

We estimate the total market as 300 million units in 2018 and anticipate a 1% annual growth rate. About half the opioid group and about a third of the non-narcotic group comprise the addressable market, which is just under half of the total.²⁸

Based on our review with management, addressable surgeries are approximately 26 million per year split between inpatient and outpatient surgeries. This excludes many of the minor surgeries for Botox or mole removal for example, where IV pain control is not used. Assuming an average of 1.5 days of treatment needed at 6 doses per day generates an addressable market of about 234 million units.

Europe has provided a benchmark for IV tramadol as the drug has been used there for many years in a surgical setting as a generic, with no marketing support. Unit penetration is 10% based on IMS Health data for the period between 2014 and 2016. If this is applied to the United States, this suggests sales of 30+ million units could be achieved.

Based on our review, we conservatively forecast that IV tramadol can launch in 2021 with about 2 million units and rise steadily over time to make up about 15 million units by 2029. From there, unit growth increases with population until the patents expire, after which we forecast a decline in volume. Our pricing model anticipates a \$15 price in 2018, rising at an inflation rate of 3.5% per year until the patent expires, at which time we anticipate a ~25% price decline.

These assumptions generate gross revenues of \$35 million in 2021 rising to \$389 million by 2032. Based on information in financial filings and management commentary, we forecast an 11% royalty to be paid to Revogenix and a ~4.5% royalty to be paid to Fortress along with a low single digit royalty and costs of manufacture to the CMO. The net of these obligations and costs are forecast to be 26% of revenues.

R&D and SG&A expenses will be near \$30 million per year as Avenue develops IV tramadol and satisfies upfront and NDA submission requirements. Following the anticipated approval of IV tramadol, we forecast R&D to drop to zero and SG&A to increase to reflect the hiring of a sales force. After NOLs are exhausted, taxes are expected to be paid at a 30% rate.²⁹

We employ a DCF model to generate our valuation and use a 15% discount rate and to these assumptions we apply a 50% probability³⁰ of ultimate commercialization of IV tramadol in the United States. Our estimates yield a target price of \$19.00 per share.

²⁸ 50% of opioids addressable + 1/3 of non-opioids addressable = 80% x (1/2) + 20% x (1/3) = 46.66%

²⁹ 2018 and forward we use a consistent 30% tax rate for our US-based companies which is a combination of federal and state rates. This reflects the 21% rate from the recent corporate tax reduction, an average 5% state rate and an additional amount to reflect our assumption that state rates will increase to compensate for less federal funding and the adjusted probability that federal rates will increase in the future.

³⁰ Clinical Development Success Rates 2006-2015. David W. Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

CONCLUSION

Avenue Therapeutics obtained the rights to develop IV tramadol in the United States to address an unmet need in the postoperative pain space. Since tramadol is a known chemical entity and the necessary pharmacokinetic and pharmacodynamic work has been done, only Phase III trials are necessary for approval and the resulting data may be submitted in an NDA using the 505(b)(2) route for approval. This means that the product can potentially generate sales in 2021.

In the current continuum of IV pain medications uses in the operational space, there is a gap in treatment for moderate to moderately severe pain. There is a strong desire by stakeholders to reduce the use of potent opioids due to the side effect, addiction and abuse potential. Contraindications with other analgesics, such as NSAIDs also create an opening where an alternative is needed. Tramadol can avoid the bleeding risk, GI effects, respiratory depression, hepatic damage and risk of dependence that can arise with the use of other analgesics. There is a large market for IV analgesics and with many patients exposed to the aforementioned obstacles, IV tramadol has a good chance of achieving material penetration. We look to the European market to get a sense of what might be possible for IV tramadol and see that the drug has achieved a 10% penetration into the IV analgesic market. Our forecasts for the US market anticipate a conservative ~4.5% penetration rate at the peak.

Key reasons to own:

- **Phase III IV Tramadol Asset with NDA Expected in 2019**
 - **IV Tramadol Fills Gap in Pain Treatment Continuum**
 - **Avoids IV Opioid and IV NSAID Contraindications**
 - **Relatively Low Potential for Abuse**
 - **Multi-modal Action**
- **Completion of Registrational Studies Anticipated in 2019**
- **505(b)(2) Route of Approval**
 - **Historically Shorter than 505(b)(1) Pathway**
 - **Historically Higher Rates of Approval vs. 505(b)(1) Pathway**
- **Pursuing Hospital Market of 300 Million Units**
- **Sufficient Cash to Complete Currently Active Trials**

In summary, we believe that the proven characteristics of IV tramadol make it a low risk pursuit for Avenue and we expect a short runway to generate registrational data and submission of an NDA. Given the strong argument for addressing a material unmet need, we anticipate a rapid uptake in the surgical setting. Based on our forecasts, the shares are undervalued relative to their potential and we initiate ATXI with a target price of \$19.00.

PROJECTED FINANCIALS

Avenue Therapeutics, Inc. - Income Statement

Avenue Therapeutics, Inc.	2017 A	Q1 E	Q2 E	Q3 E	Q4 E	2018 E	2019 E	2020 E
Total Revenues	\$0.0							
R&D	-							
R&DLicenses	\$6.7	\$4.8	\$4.8	\$4.9	\$5.0	\$19.5	\$21.5	\$1.0
G&A	\$1.1	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Other expenses	\$3.6	\$2.2	\$2.2	\$2.3	\$2.4	\$9.1	\$8.0	\$12.0
	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Operating Income	(\$11.4)	(\$7.0)	(\$7.0)	(\$7.2)	(\$7.4)	(\$28.6)	(\$29.5)	(\$13.0)
<i>Operating Margin</i>	-	-	-	-	-	-	-	# DIV/0!
Interest Expense	\$0.3	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Total Other Income	\$0.6	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Pre-Tax Income	(\$12.3)	(\$7.0)	(\$7.0)	(\$7.2)	(\$7.4)	(\$28.6)	(\$29.5)	(\$13.0)
Taxes & Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
<i>Tax Rate</i>	0%	0%	0%	0%	0%	0%	0%	0%
Net Income	(\$12.3)	(\$7.0)	(\$7.0)	(\$7.2)	(\$7.4)	(\$28.6)	(\$29.5)	(\$13.0)
Reported EPS	(\$1.85)	(\$0.68)	(\$0.67)	(\$0.69)	(\$0.70)	(\$2.74)	(\$2.72)	(\$1.13)
<i>YOY Growth</i>	-	-	-	-	-	-	-	-
Shares Outstanding	6.6	10.3	10.4	10.5	10.6	10.5	10.9	11.5

Source: Company Filing // Zacks Investment Research, Inc. Estimates

HISTORICAL STOCK PRICE



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