# at a glance™

AVENUE THERAPEUTICS



**Recent Events:** ***Avenue Therapeutics' Phase 3 program for intravenous Tramadol in the management of moderate to moderately severe postoperative pain is in high gear. The Phase 3 trial in bone surgery is set to report topline results next quarter and a Phase 3 open-label safety trial was initiated earlier this month. Submission of a NDA under provisions of 505(b)(2) and commercial launch are calendared for year-end 2019 and 2020, respectively.***

## Key Considerations

- **Avenue's lead candidate is an intravenous (IV) formulation of the popular pain drug Tramadol, now available in the U.S. only in oral pill form. More than 40 million scripts are written for it each year.**
- **The IV formulation of Tramadol is intended as an alternative to Schedule II IV narcotics in post-surgical patients suffering moderate to moderately serve pain.**
- **IV Tramadol is expected to provide pain relief similar to Schedule II narcotics, but without the often-considerable side effects of narcotics, in particular strong sedation, respiratory depression, constipation, and the risk of dependence.**
- **Importantly, Tramadol is considered to be the least addictive of all opioid drugs due to its mechanism of action. It's a Schedule IV drug vs. morphine which is Schedule II due to its addiction potential.**
- **The development timeline for IV Tramadol is expected to be relatively short. The first of two Phase 3 trials will report out 2Q18. The second Phase 3 will start 3Q18, with the NDA filing anticipated for year-end 2019.**
- **The start of a Phase 3 safety trial, which is not required for the NDA, was announced January 2, 2018 and will enroll approximately 250 patients under an open-label protocol.**
- **A large addressable market awaits IV Tramadol. Approximately 250 million units of Schedule II intravenous narcotics are prescribed annually for post-operative pain. If IV Tramadol captures just 10 percent of the U.S. market (the same as it commands in Europe with no promotion) it would generate significant revenue at modest pricing per vial.**
- **Avenue's current patent portfolio provides protection of IV Tramadol to at least 2036.**

## Avenue Therapeutics, Inc.

**(Nasdaq: ATXI)**

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| **Recent Price:** | **$5.05** |
| **Shares Outstanding:** | **10 million** |
| **Approx. MktCap:** | **$50.5 million** |
| **Fiscal Year Ends:** | **Dec. 31** |

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## Overview

IV Tramadol is expected to be well-received in the post-op setting.

Its product profile suggests it is suitable for patients with moderate to moderately severe pain who can't tolerate Schedule II narcotics, or for whom they are contraindicated.

But perhaps the biggest draw will be Tramadol's low addiction potential compared to narcotics. It would be the first viable option to hard-core narcotics for the management of moderate to moderately severe pain in the post-operative setting.

Tramadol provides pain relief similar to Schedule II narcotics, has generally more tolerable side effects, and holds a lower potential for abuse and opioid-dependency.

In current recovery-room practice, Schedule II narcotics are the only approved IV drugs for patients with moderate to moderately severe pain. Upon discharge, patients are given the pill form of the same Schedule II narcotic --generally short-acting hydrocodone or oxycodone. For several clinical reasons, doctors want patients to take the same pain med at home as they got in the hospital intravenously.

Concerns are growing about this long-standing protocol as more and more data indicates that the use of narcotics as analgesia should be avoided whenever possible.

The availability of IV Tramadol will allow a change in that protocol, potentially impacting the spiraling growth of opioid abuse.

## About Tramadol

Tramadol was developed by the German pharma company Grunenthal GmbH and licensed to Johnson & Johnson, which introduced it in the U.S. in 1995 in oral pill form. It has grown into one of the most widely prescribed drugs of all time.

The 40 million prescriptions for oral Tramadol written each year in the U.S. account for roughly 20 percent of all opioid scripts. The drug went generic in 2007.

Tramadol's popularity derives from its narcotic-like pain relief without the baggage of a narcotic.

Yes, Tramadol is an opioid, as is morphine. But because its addictive qualities are low, it's classified as a Schedule IV opioid, versus morphine which is Schedule II because of addictiveness.

## Notable & Upcoming

**-2Q17 - IPO raises $38 million in gross proceeds**

**-3Q17 - Start of first Phase 3 (bone surgery)**

**-1Q18 - Start of 'all comers' Phase 3 safety study**

**-2Q18 - Top-line first Phase 3 (bone surgery)**

**-3Q18 - Start of second Phase 3 (soft tissue surgery)**

**-2Q19 - Top-line second Phase 3 (soft tissue surgery)**

**-4Q19 - File for abbreviated 505(b)(2) FDA approval**

**-2020 - Anticipated product launch**

### An Alternative to Post-Op Schedule II Drugs

The pain medication patients are sent home with after surgery is almost always decided by the pain medication they receive intravenously in the recovery room. Physicians keep patients on the same drug in pill form unless side effects dictate otherwise.

Since Tramadol isn't currently approved in IV form, physicians don't often prescribe Tramadol as the take home pain med.

They have no current alternative but to prescribe addictive Schedule II narcotics for moderate to moderately severe pain in IV form in the recovery room, and in pill form upon discharge.

That may soon change.

The availability of IV Tramadol will allow a change in protocol, to replace addictive narcotics with Tramadol and potentially impact the growth of opioid abuse and dependency.

Tramadol is judged by the DEA to be inherently less additive than Schedule II narcotics. Patients given IV Tramadol in the recovery room, will almost always be prescribed the oral pill form upon discharge, avoiding exposure to Schedule II narcotics.

The other main feature of Tramadol vs. Schedule II narcotics is what is generally held to be a more tolerable side effect profile. Schedule II narcotics are associated with strong sedation, respiratory depression, extended constipation, and risk of dependence.

Tramadol is not without side effects. It can cause nausea and dizziness, and it is contraindicated for patients with a history of seizure and those on serotonergic drugs.

***Tramadol is considered to be the least addictive of all opioid drugs due to its mechanism of action. It's a Schedule IV drug vs. morphine which is Schedule II due to its addictiveness.***

Narcotic-like pain relief without the narcotic-like potential for addiction—how is that possible?

Tramadol is not the typical opioid. Schedule II narcotics work by heavily binding to opioid receptors in the 'feel good' region of the brain, and in the gut as well which, by the way, is why they are associated with sometimes debilitating constipation.

Tramadol, on the other hand, binds weakly to opioid receptors, getting much of its pain-relief power by inhibiting the re-uptake of norepinephrine and serotonin, a non-opioid mechanism. The result: narcotic-like pain relief with less addiction potential and a better safety profile.

There's no known clinical reason why IV Tramadol if approved in the U.S couldn't be prescribed for most post-op patients with moderate to moderately severe pain. It will be especially beneficial for patients contraindicated for NSAIDs, people with poor cardio-pulmonary function, obese patients with sleep apnea, those intolerant of strong narcotics and the elderly at risk for respiratory depression.

### Phase 3 Clinical Program

Avenue will do two Phase 3 clinical trials, one in bone surgery and the other in soft tissue surgery. This is the standard way in which the FDA likes to see pain medicines studied.

The first Phase 3 was initiated 3Q17. It will report topline 2Q18, less than a year from now. The second will start shortly thereafter and report topline 2Q19.

The two trials will prepare the company for the filing of a New Drug Application (NDA) 4Q19. If everything stays on plan, expect product launch in 2020.

The outcome for each Phase 3 trial will be standard measures of pain relief with IV Tramadol vs. placebo during the first 48 hours after surgery.

The first Phase 3 will recruit up to 405 patients undergoing surgery to remove disfiguring foot bunions in a procedure called a bunionectomy.

The condition is generally caused by frequent wearing of challenging footwear, like extreme high heels. Eighty percent of the procedures are done on women. It involves cutting, removal and realignment of foot bone. It is universally described as one of the most painful surgeries.

***"Early opioid prescribing patterns for opioid-naïve patients have been found to be associated with the likelihood of long-term use."***

*- Centers for Disease Control and Prevention*

Upon completion of surgery, the patients will be randomly assigned to one of three blinded arms to receive post-operative analgesia for 48 hours of either 25 mgs IV Tramadol, 50mgs IV Tramadol, or placebo.

The second Phase 3, the soft tissue study, will enroll up to 360 patients undergoing an abdominoplasty, or tummy tuck.

The FDA considers tummy tucks an excellent pain model because they require a hip-to-hip incision through soft tissue, a procedure generally regarded as extremely painful.

Patients will be randomized to three arms for blinded treatment with either 50 mg IV Tramadol, morphine, or placebo. The outcome comparator is placebo. The morphine treatment arm is to gain data that may be useful in product marketing.

Simultaneously with the Phase 3 program, Avenue will be conducting an 'all comers' safety study of approximately 250 patients. This is separate from any requirement by the FDA for marketing approval.

## Summary Points

- **IV Tramadol is expected to be the first pain medication to take the place of addictive Schedule II narcotics in post-operative moderate to moderately severe pain.**
- **Avenue will do two pivotal clinical trials to gain FDA marketing approval -- one in bone surgery, the other in soft tissue. Placebo is the control comparator in both trials.**
- **Expect results from the first Phase 3 in less than a year from now, followed by the soft tissue Phase 3 results in 2Q19, an NDA filing 4Q19, and product launch in 2020.**
- **A sizable U. S. addressable market awaits IV Tramadol. A modest 10 percent penetration could generate annual revenue in the range of $250-$300 million.**
- **Current patent coverage extends to 2036, protecting the dosing protocol, maximum concentration and time-denominated blood levels of the drug.**

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