Revive Therapeutics Ltd (TSXV: RVV) - $0.13 / Share

Revive Initiates Bucillamine Phase 2 Study, Expands Focus To Include Cannabinoid Research

In early February 2017, Revive Therapeutics (TSXV: RVV) announced the initiation of a Phase 2 study examining bucillamine as a treatment for cystinuria. This is an important milestone for the company, as bucillamine is the company's lead development candidate. Last month, Revive announced an expansion of the company's focus to include research and discovery of cannabinoid-based therapeutics. The company appointed Dr. Pritesh Kumar as Scientific Advisor for this effort.

Expansion into cannabinoid research is not a big stretch for Revive; the company's mission statement remains largely unchanged. Revive is still focused on advancing novel treatment options for serious and unmet medical needs, with an eye on repurposing proven safe and effective therapeutic agents for rare and orphan diseases. This is evidenced by the initiation of the Phase 2 bucillamine study noted above. However, cannabinoids also fit the model perfectly, and offer potential as both standalone and adjunct therapy treatments for many of the same unmet medical needs Revive has experience targeting through clinical and preclinical development.

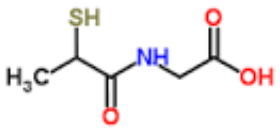
Below is an on bucillamine and the Phase 2 initiation, as well as an introduction to the company's strategy in expanding the pipeline through cannabinoid research.

Revive's Mission & Bucillamine Update

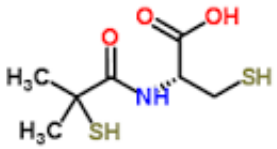
Revive Therapeutics' missions statement is to advance novel treatment options for serious and unmet medical needs. Over the past few years, the company's focus has been on finding known safe and effective agents approved outside the U.S. and repurposing these medicines for orphan diseases through the U.S. 505(b)(2) approval process. Bucillamine is the company's leading clinical-stage candidate. The drug is a dithiol derivative of tiopronin for the treatment of cystinuria.

Tiopronin, a monothiol, is sold as Thiola® by Retrophin, Inc. for the treatment of cystinuria. Revive's clinical hypothesis is that bucillamine should be more effective than Thiola at similar doses, potentially allowing Revive to expand the roughly $250 million U.S. cystinuria market, or equally as effective at substantially lower doses, which would allow for improved safety and tolerability - potentially even a lower cost - resulting in big market share gains for Revive.

Chemical Structures of tiopronin & bucillamine



THIOLA® (tiopronin)



(bucillamine)

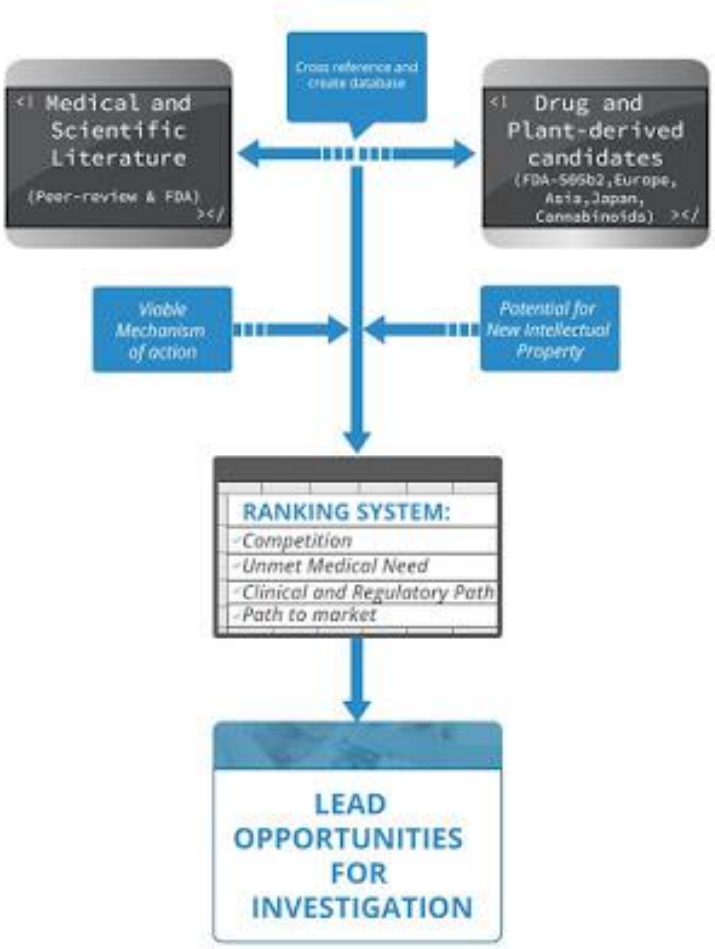
Japanese researchers have tested this theory in a small head-to-head study. Results demonstrated that bucillamine was statistically superior (markedly superior in two patients and slightly superior in the third) to Retrophin's $150 million Thiola. Bucillamine is a drug that has been approved and used in Japan for over three decades, mostly for the treatment of rheumatoid arthritis (RA). Ayumi Pharma of Japan reported 57 million tablets sold in 2015. Recent data confirm the efficacy of bucillamine in RA, as well as other oxidative conditions such as cisplatin-induced ototoxicity and transplantation-associated reperfusion injury. Revive has previously studied bucillamine in a Phase 2 study in patients with gout, demonstrating efficacy comparable to Takeda's Colcrys®. Importantly, bucillamine has an "A" safety rating from the Japanese Ministry of Health.

On February 7, 2017, Revive initiated a Phase 2 multicenter, open-label, sequential dose escalation clinical study of bucillamine as a treatment for cystinuria. Target enrollment for this study is 30 subjects. Over the past two months, the company has announced participation in this study by the NYU School of Medicine and the Massachusetts General Hospital. Bucillamine will be dosed for seven days, with follow-up for safety and tolerability at day 14. The primary outcome measures will be the incidence of treatment-emergent adverse events, with secondary outcome measures in 24-hour urine cystine excretion and 24-hour urine cystine capacity.

Management's goal is to complete the study in the second half of 2017 and then hold an end-of-Phase 2 meeting with the U.S. FDA shortly thereafter to discuss the pivotal study design. Following successful completion of the Phase 2 program, I believe management will seek to sign a development partnership with a larger pharmaceutical organization interested in commercializing bucillamine for cystinuria and/or gout.

Revive's Approach To Drug Discovery

To expand the pipeline beyond bucillamine for cystinuria, Revive is currently deploying a multi-disciplinary drug candidate screening process that includes complex bioinformatics and research collaborations with leading academic institutions. The bioinformatics platform was specifically designed to identify repurposed and innovative drug treatments for serious and unmet medical needs. The company reviews scientific literature looking for mechanisms of action that could prove useful for diseases. Management and its advisors then rank these drug-disease pairs based on a weighting system that incorporates clinical studies, FDA correspondence, competition, and unmet medical need.

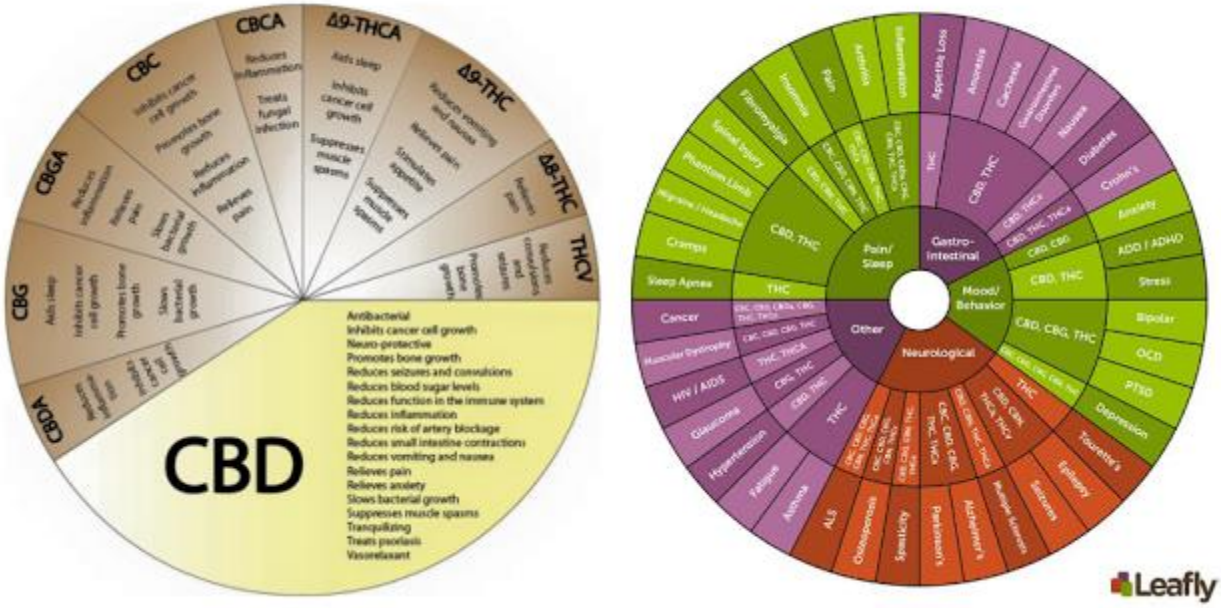


To date, Revive has identified a number of repurposed drug and plant-derived candidates, such as cannabinoids, that warrant further screening. Management is currently focusing its research efforts on cannabis-derived or cannabis-related drug candidates, including CBD and THC derivatives. The company believes this strategy offers the potential for development of highly differentiated drug candidates that are superior to current standards of care, as well as new intellectual property through the combination of repurposed drug candidates and cannabis-related drug candidates.

Why Cannabinoids Make Sense

The endocannabinoid system (ECS) is a group of endogenous cannabinoid receptors located in the mammalian brain and throughout the central and peripheral nervous systems, consisting of neuromodulatory lipids and their receptors. Two primary endocannabinoid receptors have been identified: CB1 and CB2. These receptors are crucial to bioregulation, with important roles in paracrine and autocrine cell-signaling.

The cannabinoid signaling system has recently garnered attention as a therapeutic target for numerous indications, and cannabinoids are now being pursued as new treatment options in diverse medical fields such as neurology, gastroenterology, pain management, and oncology (Hardman JM *et al.*, 2017). Over 70 cannabinoids produced by *Cannabis sativa* have been identified, including cannabidiol (CBD), cannabinol (CBN), Δ9-tetrahydrocannabinol (Δ9-THC), and cannabidivarin (CBDV). Many of these candidates have proven anti-epileptic, anti-psychotic, analgesic, and neuroprotectant properties.



Some synthetic cannabinoids have been commercialized, including Marinol® (dronabinol) by AbbVie and Cesamet® (nabilone) by Valeant/Meda, both approved as anti-emetic agents. GW Pharma is developing two cannabinoid drug candidates, Epidiolex® for the treatment of refractory epilepsy in pediatric patients and Sativex® for spasticity and neuropathic pain associated with multiple sclerosis. Sativex is approved in 30 countries outside the U.S., including Canada.

- Legislative Tailwind -

In December 2016, former President Barack Obama signed into law the 21st Century Cures Act. The Cures Act, which is designed to facilitate FDA approval of new drugs and medical devices, is a major win for the cannabis industry. The Cures Act will enhance current FDA programs and allow for a quicker path for breakthrough pharmaceutical products targeting debilitating diseases with limited alternative treatment options. That's nearly identical to Revive's mission statement!

The Cures Act directs the U.S. FDA to make decisions based on the use of "real world evidence" for approval of new indications for FDA-approved drugs. The use of observational studies, patient input, anecdotal data, and other retrospective research greatly reduces the cost and time to market compared to conducting large randomized clinical trials. This should increase the odds of success as the FDA may focus less on objective measures and prohibitively expensive placebo-controlled randomized clinical trials. A repurposed drug like bucillamine, already approved and used for three decades outside the U.S., targeting an ultra-rare orphan condition such as cystinuria, looks to be the exact type of medicine the Cures Act was put into place to expedite. As such, Revive is well-positioned to benefit from this sweeping legislative action.

Cannabinoid therapeutic agents look equally well-positioned, as there is substantial empirical and real-world evidence of safety and therapeutic effect. Over the past three years, the U.S. FDA has granted orphan disease designation 17 times to cannabis-derived products. Target indications include Dravet syndrome, cystic fibrosis, systemic sclerosis, infantile spasms, Lennox-Gastaut syndrome, glioma, glioblastoma multiforme, graft vs. host disease, and Fragile X syndrome.

The U.S. government is making an effort to streamline the drug approval process for "known safe and effective" medications by passing the 21st Century Cures Act. By expanding its focus to include cannabinoids and other plant-based therapeutics, Revive greatly enhances the pool of drug candidates that fit its mission statement. An expanded focus means more shots on goal, potentially greater access to funding, and hopefully value creation for shareholders.

Conclusion

Dr. Kumar's background will be instrumental in helping Revive tackle this new expanded approach. Dr. Kumar is a pharmacologist with expertise in current cGMP pharmaceutical products and Active Pharmaceutical Ingredient (API) development. He is the CEO of PhytoSciences, an international organization comprised of 40+ global scientists/physicians based in India, Africa, Canada, and the U.S. His company consults in the areas of R&D, clinical trial solutions, and pharmaceutical manufacturing as it pertains to cannabinoid-based therapeutics. This expertise and PhytoSciences' network of knowledge, coupled with Revive's bioinformatics discovery algorithm, should allow Revive to get additional shots-on-goal as noted above.

In the meantime, bucillamine development for cystinuria is moving forward in Phase 2. I'm excited to see that program get underway. Top-line data are expected later this year. I'm equally as excited to see what the company has planned for its cannabinoid efforts. I think there is real synergistic potential between cannabinoids and other repurposed agents for rare diseases, including dual-targeting kidney stones with bucillamine. Revive's efforts will likely focus on rare kidney or liver disorders where there is the potential for orphan disease designation.

Company's such as GW Pharmaceuticals have been able to advance THC and CBD candidates to commercialization and into late-stage clinical development such that its market capitalization now eclipses $3.1 billion in value! This is the path Revive would like to head down over the next few years by advancing its pipeline and expanding efforts into cannabinoid research.

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