

Restoring Nerve Function to Treat Diabetic and Other Peripheral Neuropathies

Regenacy Pharmaceuticals, LLC is positioned to deliver a superior, first-in-class treatment for peripheral neuropathies, which affect many millions of people, including over 50% of diabetic patients. Our lead compound ricolinostat (ACY-1215) is an oral, selective inhibitor of the microtubule-modifying enzyme HDAC6 that is ready to enter phase 2 clinical trials following a favorable regulatory review by the FDA's Analgesia, Anesthesia and Addiction Products Division.

Our focus on ricolinostat for diabetic, chemotherapy-induced, and inherited peripheral neuropathies is based on compelling proof-of-concept preclinical studies demonstrating restoration of normal nerve function.

Ricolinostat has previously completed Phase 1 and 2 clinical trials in multiple myeloma, comprising experience in 250+ patients including use as a single agent and in combination with various anticancer agents. **Ricolinostat has demonstrated an excellent safety and tolerability profile in clinical trials, including healthy volunteers, compared to the high toxicity of currently marketed pan-HDAC inhibitors (e.g. vorinostat, panobinostat).**

Ricolinostat is protected by issued US and foreign composition of matter patents through 2034 with additional method-of-use patents positioned to issue for diabetic, chemotherapeutic and inherited neuropathies, as well as polycystic kidney disease.

Regenacy was founded in December 2016 following the acquisition of Acetylon Pharmaceuticals by Celgene. Regenacy received exclusive rights to ricolinostat for a range of non-cancer disease indications.

- Unique disease-modifying capability to restore nerve function in peripheral neuropathy
- Phase 2-ready lead program (ricolinostat) in diabetic peripheral neuropathy to treat pain and numbness
- Potential breakthrough treatment in chemotherapy induced neuropathy and Charcot-Marie-Tooth Disease
- Validated HDAC1,2 inhibitor program aimed at hematologic cancers, hemoglobinopathies and cognitive dysfunction

Regenacy has an unparalleled portfolio of isoform selective HDAC1/2 inhibitors, with potential application in oncology (AML), cognitive dysfunction (Alzheimer's Disease, depression and schizophrenia), and hemoglobinopathies (sickle cell and beta thalassemia).

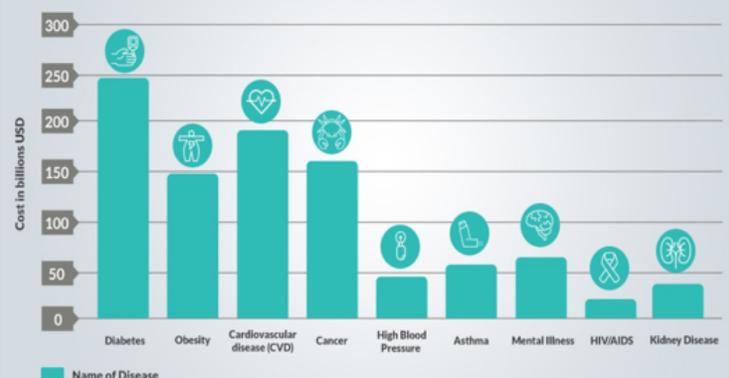
Regenacy's isoform selective HDAC1/2 inhibitors are differentiated from pan-Class I (i.e. HDAC1/2/3) inhibitors by superior preclinical safety and tolerability profiles, and they include both blood-brain barrier penetrant and non-penetrant preclinical candidates formulated for oral administration as tablets, with excellent pharmacokinetic properties.

Diabetic Peripheral Neuropathy is a Huge and Growing Health Issue World Wide

Diabetes and related health issues are the leading medical cost in the United States. Diabetic peripheral neuropathy (DPN) is one of the most common complications of type 1/type 2 diabetes and can impact over 50% of diabetics. DPN causes burning pain, tingling and numbness in the hands and feet leading to increased morbidity and mortality as a consequence of limb amputation. Current treatments are (a) only effective in < 30% of patients with pain symptoms, (b) provide limited pain relief, (c) do not address numbness, (d) are not well tolerated, and (e) can lead to addiction (opioid use).

There are an estimated 35M+ people in Asia, US and EU impacted by DPN and this estimate is expected to dramatically increase in the next 10+ years. Total current market size is estimated to be over \$10B for drugs that provide symptomatic relief of pain only, and greater potential for a **first-in-class disease-modifying therapy**. A further estimated 500,000 patients suffer from chemotherapy induced peripheral neuropathy (CIPN) and approximately 100,000 from Charcot-Marie-Tooth (CMT) disease and related inherited neuropathies.

Cost of Diabetes vs Other Medical Conditions in the US



Broad, Maturing Portfolio of Selective HDAC Inhibitors

PRODUCT CANDIDATE	LEAD OPTIMIZATION	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3
Peripheral Neuropathy - HDAC6 Inhibitors					
Ricolinostat	Diabetic Neuropathic Pain				
Ricolinostat	Diabetic Neuropathy (Pain and Numbness)				
Ricolinostat	Charcot-Marie-Tooth Disease (Type 2)				
HDAC1/2 Inhibitors - Therapeutic Opportunities					
Lead RCY-1410	Hematologic Cancers				
Discovery Program	Neurodegeneration / Psychiatric / Other				
Discovery Program	Hemoglobinopathies				

Robust Preclinical Proof-of-Concept with Selective Deacetylase Inhibitors

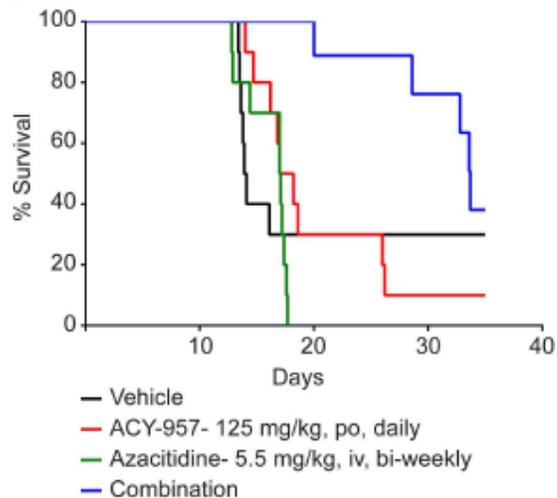
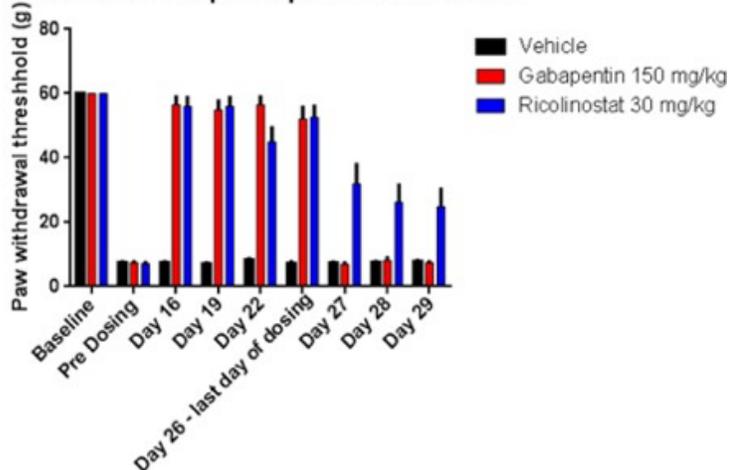
Ricolinostat can restore fast axonal transport in multiple animal models of peripheral neuropathy, both genetic and induced forms. Injury and loss of axons (axonopathy) is a common clinical feature found in these animal models, and in patients with distal (hands and feet) symmetric polyneuropathy due to diabetes, chemotherapy and genetic mutations (CMT).

Ricolinostat reverses established diabetic neuropathic pain within hours of dosing (panel). The effect is similar to approved pain treatments (analgesics), gabapentin and pregabalin. Unlike standard analgesics the effect persists for days after drug dosing has stopped (panel – days 27-29) suggesting disease-modification. Ricolinostat reverses chemotherapy (e.g. taxane and cisplatin) induced neuropathy, both pain and numbness, through the regrowth of epidermal nerve fibers ([Krukowski et al. PAIN, 2017](#)). Ricolinostat restores motor function and nerve conduction velocity in a mouse models of Type 2 Charcot-

Marie-Tooth disease ([Mo et al, Nature Communications, 2018](#); [Benoy et al, Brain, 2018](#); [Benoy et al, Neurotherapeutics, 2016](#); [d'Ydewalle et al, Nature Medicine, 2011](#)).

Selective HDAC1/2 inhibition shows impressive efficacy in cell based and animal models of hematologic cancers. These compounds have similar efficacy as pan-selective HDAC inhibitors with significantly reduced toxicity. HDAC1,2 inhibitors work well in combination with standard of care treatments such as azacitidine for AML, (bottom right) (as shown in [Min et al, PLOS One, 2017](#)) and emerging cancer treatments like EZH2 inhibitors (as shown in [Johnson et al, Oncotarget, 2015](#)). In addition, brain penetrant HDAC1,2 inhibitors improve cognitive function in mouse models of Alzheimer's disease. Several lead drug candidates have been identified (ACY-1410 and others) for additional preclinical validation and entry into IND enabling studies.

Reversal of neuropathic pain in diabetic rats



Leadership Team With Extensive Neurology, Hematology & Small Molecule Expertise

MANAGEMENT TEAM

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- Expert in endocrinology

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