Rezolute, Inc.
www.rezolutebio.com

Targeting rare and metabolic diseases with transformative therapies

Clinical-stage biopharmaceutical company Rezolute, Inc., is developing transformative therapies for rare and metabolic diseases. The company's lead phase 2 candidate RZ358, a monoclonal antibody (mAb) to treat hypoglycemia caused by congenital hyperinsulinism (CHI), has received orphan designation in both the US and Europe and is now on the path to potentially becoming a universal treatment for the disorder.

At the beginning of the twentieth century, a British physician named Archibald Garrod was studying a rare disease called alkaptonuria, a congenital condition in which the body cannot properly process the amino acids phenylalanine and tyrosine, leading to the buildup of toxic by-products. After observing how alkaptonuria was passed on in families, Garrod proposed that this disease and similar 'inborn errors of metabolism' were caused by a defective gene producing a malfunctioning enzyme.

Today, a century after the 'one gene–one enzyme' idea was conceived, the genetic basis of dozens of congenital diseases affecting metabolism is well understood. One such condition is congenital hyperinsulinism (CHI), a rare but devastating disorder characterized by dysregulated insulin metabolism that leads to chronic and dangerous hypoglycemia.

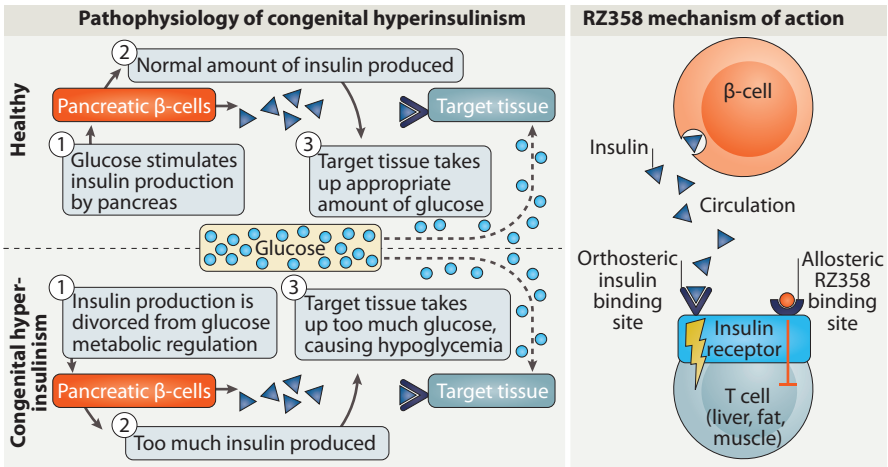
Like many orphan diseases, CHI presents an unmet medical need. Rezolute, Inc., a clinical-stage biopharmaceutical company, is currently developing a novel CHI therapy to fill this need, along with therapies for other common metabolic disorders.

Rezolute targets known mechanisms of action and established genetic pathways to develop transformative therapies for both rare and common conditions. The company's portfolio has three novel and potential first- and best-in-class compounds in development.

RZ358, the lead asset and program, is a monoclonal antibody (mAb) for the treatment of hypoglycemia caused by CHI. RZ358 acts as a negative allosteric modulator of insulin at its receptor on insulin-dependent target tissues, and as such is uniquely suited as a potential universal treatment for all forms of CHI. It has been investigated in several clinical trials, including a phase 2a study in adults and children with CHI, and is currently in late phase 2 clinical development.

RZ402 is a plasma kallikrein inhibitor for retinal-vascular complications of diabetes mellitus such as diabetic macular edema, a leading and growing cause of blindness in working-age adults. RZ402 is being developed as a once-a-day pill, and in animal models it demonstrated benefit comparable to that of the current standard-of-care anti-VEGF therapies, which in contrast are administered by injection into the eye. Rezolute intends to begin clinical trials with RZ402 in mid-2020.

AB101 is a long-acting (weekly) subcutaneous depot formulation of native human insulin that is in a phase 1 clinical trial to support indications in diabetes mellitus.



	Standard of care	RZ358
Development	Not developed for CHI	Tailored specifically for CHI
Targeting	Only targets insulin production by pancreatic β-cells	Targets insulin receptor/signal on insulin-dependent target tissue
Relevancy	Genetic-dependent, narrow targeting	Potentially universal treatment
Impact	Marginally effective, invasive, and/or significant side effects	Reversibly counteracts insulin only when insulin is elevated

Fig. 1 | Pathophysiology of CHI and mechanism of action of RZ358. Excessive and unregulated insulin secretion from pancreatic β-cells occurs in CHI, which leads to increased insulin action at target tissues such as muscle, fat and liver and consequently low blood glucose, or hypoglycemia (left). RZ358, tailored for CHI, binds to an allosteric site on the insulin receptor on a broad variety of target tissues, including muscle, fat and liver, where it reduces intracellular signaling that leads to glucose uptake (right).

Augmenting this portfolio, Rezolute's leadership team brings decades of collective scientific, development, and business experience to support the goal of providing new and effective treatments for rare and metabolic diseases to healthcare stakeholders.

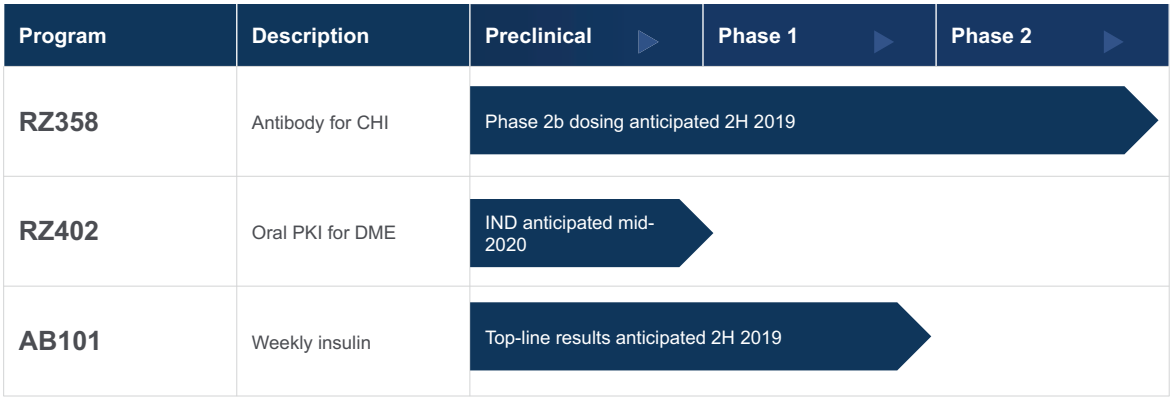
Anchored by its late-stage RZ358 program and led by an experienced team, Rezolute's pipeline provides multiple near-term inflection points over the next several years.

Rare and devastating

CHI is a rare genetic disease with orphan designation that affects roughly 1 in 50,000 to 30,000 live births globally, although in some populations the incidence is as high as 1 in 2,500. CHI arises from one or more of at least eleven known mutations that cause excessive and unregulated insulin secretion from pancreatic β-cells. This leads to increased insulin action at target tissues such as muscle, fat and liver and consequently low blood glucose, or hypoglycemia (**Fig. 1**).

Despite being a rare disease, CHI is the leading cause of persistent hypoglycemia in children. CHI usually presents at birth or within the first year of life with nonspecific symptoms or signs, including but not limited to flaccidity, feeding issues, irritability, lethargy and cyanosis (blue–purple discoloration of the skin and mucous membranes caused by low oxygen saturation of the underlying tissues).

Glucose is the predominant source of energy for the brain, and when the brain does not receive adequate amounts of glucose it may use alternative fuels such as ketone bodies to support metabolism. In CHI, owing to increased insulin action at target tissues, ketone bodies are suppressed, and this 'double hit' leaves the brain particularly vulnerable to metabolic starvation. Short- and long-term neurologic complications of hypoglycemia due to CHI may include developmental delays, learning disabilities, behavioral issues, seizures, coma or even death. Up to 50% of all patients are believed to have one or more long-term neurological complications of CHI.



Multiple near-term inflection points anchored by a late-stage orphan drug program

Fig. 2 | Rezolute's diversified pipeline at multiple stages of development. DME, diabetic macular edema; PKI, plasma kallikrein inhibitor.

Approximately half of all cases of CHI are caused by mutations in two genes (*ABCC8* and *KCNJ11*) that encode functional protein subunits of the ATP-sensitive potassium channel within the pancreatic β-cells. CHI presents as two main forms: a focal version, in which a discrete and specific area of the pancreas is affected, and a diffuse version that affects the entire pancreas. Both forms lead to dysregulated insulin secretion, and their biochemical pathophysiology and clinical presentation are similar.

In treating both forms of CHI, the fundamental goal is to reduce insulin levels, stabilize blood glucose and prevent brain damage. Acute or emergent low blood glucose can be treated in the short term with intravenous or enteral dextrose administration, frequent oral or enteral feeding and glucagon administration. For long-term management of CHI, the first-line therapy is usually diazoxide, a potassium channel activator. Diazoxide, however, is ineffective in approximately half of all CHI patients because its mechanism of action depends on a functional KATP channel, which is impaired by the most common mutations leading to CHI. Diazoxide also frequently produces harmful side effects, including pulmonary hypertension, changes to phenotypic facial features, hypertrichosis (excessive hair growth), fluid retention and poor taste.

In patients with focal disease who do not respond well to first-line therapy, surgical removal of the affected portion of their pancreas may be curative. Patients with diffuse disease who do not respond to first-line therapy are usually moved on to second-line treatment with somatostatin receptor agonists such as octreotide and lanreotide. If this is unsuccessful, patients with diffuse CHI may need to undergo a near-total pancreatomy, after which they may require continued medical management for hypoglycemia and repeat resection of residual tissue, before eventually developing insulin-dependent diabetes mellitus (endocrine pancreatic insufficiency) and impairment in food digestion (exocrine pancreatic insufficiency), as a result of removal of the pancreas.

An observational study conducted by Rezolute has revealed the unmet need of CHI patients, even those being treated. In this study, blood glucose was continuously monitored in 22 CHI patients, 15 of whom were receiving current standard of care, over a two-week period. Patients were found to spend an average of three hours each day with blood glucose below 70 mg/dL, the defining line for hypoglycemia. Younger children were especially vulnerable to hypoglycemia: patients 2 to 6 years of age spent an average of >220 minutes daily with blood glucose below the 70 mg/dL threshold, and a significant amount of time with even lower blood glucose levels (an average of 80 minutes at <60 mg/dL and 24 minutes at <50 mg/dL).

Restoring metabolic balance

In this landscape of marginally effective, potentially harmful or invasive therapies, Rezolute's lead candidate—the fully humanized mAb RZ358—has the potential to become a truly transformative therapy. RZ358, unlike today's standard drug treatments, has been specifically developed for CHI, with a novel mechanism of action that has major advantages for management of the disorder. In contrast to therapies such as diazoxide, which act only on pancreatic β-cells, RZ358 binds to an allosteric site on the insulin receptor on a broad range of target tissues, including muscle, fat and liver, where it causes blunting of insulin binding and intracellular signaling that leads to glucose uptake in these target cells (**Fig. 1**). By targeting these tissues rather than β-cells, RZ358 represents a potential universal therapy for treating CHI regardless of the specific genetic etiology. RZ358 is currently being developed as a biweekly intravenous therapy, and having completed phase 1 and 2a studies is now entering phase 2b trials. Phase 1 pharmacokinetic studies of single intravenous doses of RZ358 at 0.1 to 9 mg/kg in healthy volunteers revealed dose-dependent pharmacokinetics with a half-life of 15 days, supporting the biweekly dosing approach. In healthy volunteers, RZ358 prevents hypoglycemia induced by insulin administration, without producing hyperglycemia. This effect shows a pharmacokinetic-pharmacodynamic (dose–response) correlation, with the hypoglycemia-blunting effects of RZ358 lasting for two weeks.

Pharmacokinetic results from phase 2a studies in patients with CHI are consistent with those in healthy volunteers. CHI patients aged ≥12 years in Europe and ≥18 years in the US, who at baseline spent differing percentages of time with blood glucose <70 mg/dL, received a single intravenous dose of 1 to 9 mg/kg RZ358. Across this variable group of patients, RZ358 nearly normalized glucose levels to within the target range of 70–180 mg/dL, and these beneficial effects persisted for up to four weeks after a single dose. Crucially, there was no evidence of hyperglycemia, even among patients who were not initially in a hypoglycemic state. These results show proof of mechanism, in that the effects of RZ358 are disease dependent, correcting hypoglycemia when needed but not pushing patients into a hyperglycemic state. Rezolute is advancing the development of RZ358 and is now close to initiating a phase 2b trial. This open-label, repeat dose-ranging study will be conducted in CHI patients ≥2 years old with baseline substantial baseline hypoglycemia. The study is enrolling four sequential dosing cohorts, each with six to eight patients, starting at 3 mg/kg and increasing to as high as 12 mg/kg in the final cohort, as needed and tolerated. Patients will receive RZ358 for two months and continuous glucose monitoring will be used as one of several ways to evaluate the efficacy of the study drug.

The nature of the study design (sequential cohorts and open-label) offers potential opportunities for interim results as the study proceeds. Rezolute plans an initial interim data analysis in mid-2020 and another toward the end of 2020, and expects top-line overall results sometime in 2021.

RZ358, with its novel mechanism of action, has truly first-in-class and best-in-class potential. By targeting insulin-dependent target tissues and counteracting the effects of insulin only when elevated, RZ358 represents a universal treatment for CHI that avoids the concern of induced hyperglycemia. RZ358 has orphan designation in the US and Europe, and Rezolute believes that, as a potential treatment for a rare pediatric condition, the program would, upon approval, qualify to receive a Priority Review Voucher.

Rezolute's leadership is deeply involved with the CHI community and regularly meets with children carrying the burden of current CHI drug therapies, their worried parents and physicians who repeatedly stress the need for novel drug therapies. Rezolute is determined to deliver a transformative therapy to all CHI stakeholders.

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