

Investigational Therapies for HCU

Expected Development Time-Lines Informed by General Industry Assumptions. These time-lines have not been confirmed by the program sponsors.

Concept	Program	Status	2017	2018	2019	2020	2021	2022		
Gene Therapy Gene Correction	AAV8-CBS - Gene Transfer of CBS	Pre-Clinical: Proof of Concept								
	Warren Kruger, Fox Chase, Ron Crystal, Weill Cornell	Results expected 4Q18 (AAV8,)	Discovery Status - Time Lines cannot be predicted							
	E1E3E4-deleted adenoviral vector AdCBS Liver Gene Transfer	Pre-Clinical: Proof of Concept								
	Bart de Geest; Catholic Univ of Leuven	Contingent on obtaining a clinical grade vector	Discovery Status - Time Lines cannot be predicted							
Enzyme Replacement Therapy	PEG-CBS	IND Preparation								
	Orphan Technologies/ Jan Kraus, University of Colorado	Phase I enrollment to begin 4Q18	IND Studies	R	Phase I Trial	DA	R	Phase II/III Trial	DA	R
Substrate Removal	AEB4104, rh Homocystinase	Pre-Clinical: Proof of Concept								
	Aeglea Biotherapeutics	Mouse study to be presented 3Q18	Time Lines Unknown							
	Erymethionase , Methionine-y-lyase (MGL)	Pre-Clinical: Proof of Concept								
	Erytech	Initial results presented 3Q17; on hold	Pre-Clinical Proof of Concept	IND - Enabling Tox Studies		R	PIb/IIa		R	Phase II/III

Legend: DA: Data Analysis, IND: Investigational new drug; L: Market Launch; R; Regulatory Review (FDA, EMA or IRB);

Investigational Therapies for HCU

Expected Development Time-Lines Informed by General Industry Assumptions. These time-lines have not been confirmed by the program sponsors.

Concept	Program	Status	2017	2018	2019	2020	2021	2022
CBS Enzyme Activator	Heme arginate	In vitro proof of concept for CBS deficiency						
	P. Melenovská, V. Kozich & Team, University of Prague	Approved for Porphyria	On Hold - Drug Discovery Program Required					
	Arimoclomol Precursor (Bimoclomol)	Pre-Clinical: Limited proof of concept in initial pre-clinical studies						
	Warren Kruger, Fox Chase, Philadelphia (Chaperone)	Biclomol and low dose bortezomib in pre-clinical proof of concept study funded by NORD	Pre-Clinical - Feasibility to be determined Time lines cannot be predicted					
	Bortezomib	Pre-Clinical: Proof of Concept for CBS Deficiency						
	Warren Kruger, Fox Chase, Philadelphia (Proteasome Inhibitor)	Positive results shown in mouse model	Pre-Clinical Proof of Concept Unlikely to have appropriate Risk - Benefit for chronic therapy of CBS					
	SAM Allosteric Activator	Discovery Stage: Target Identification & Validation						
	IM Mendes; University of Lisbon	Targets regulatory domain for CBS	Discovery Status - Time lines cannot be predicted					
CBS Enzyme Activator	SAM Kinetic Stabilizer of SAM Domain	Discovery Stage: Target Identification & Validation						
	T. Majtan, University of Colorado	Recent grant to test SAM analogs in in-vitro and in-vivo models	Discovery Status - Time lines cannot be predicted					
	Cysteamine & mercaptoethylguanidine (MEG)	Pre-Clinical: In vitro proof of mechanism						
IM Mendes, University of Lisbon; H. Blom, University of Freiburg	Targets Arg to Cysteine Variant	Program Status & Time Lines Unknown						
Metabolic Pathway Modification	Sulfur amino acids dietary modulation	Pre-Clinical: Proof of Concept						
	Viktor Kozich, University of Prague	Needs validation in clinical trial	Requires funding and sponsor for a clinical trial Time Lines cannot be predicted					
	Taurine	Pilot Trial completed for CBS						
	J.L. van Hove, Ken Maclean, University of Colorado	Positive effects with abnormal endothelial function	Time Lines Unknown					
Metabolic Pathway Modification	Formate	Preclinical study underway with betaine						
	Ken Maclean, University of Colorado	Grant from HCU Networks America & Australia	Time Lines Unknown					

Legend: DA: Data Analysis, IND: Investigational new drug; L: Market Launch; R: Regulatory Review (FDA, EMA or IRB);