

# 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	<b>AAV8-CBS - Gene Transfer of CBS</b>	Pre-Clinical: Proof of Concept	Discovery Status - Time Lines cannot be predicted							
	Warren Kruger, Fox Chase, Ron Crystal, Weill Cornell	3Q17 (AAV8, TBG promoter & liver targeting)	Discovery Status - Time Lines cannot be predicted							
	<b>E1E3E4-deleted adenoviral vector AdCBS Liver Gene Transfer</b>	Pre-Clinical: Proof of Concept	Discovery Status - Time Lines cannot be predicted							
	Bart de Geest; Catholic Univ of Leuven	Contingent on obtaining a clinicalgrade vector	Discovery Status - Time Lines cannot be predicted							
Enzyme Replacement Therapy	<b>PEG-CBS</b>	IND Preparation	Discovery Status - Time Lines cannot be predicted							
	Orphan Technologies/ Jan Kraus, University of Colorado	May enter clinical trials in early 2018 (KOL Feedback)	IND Studies	R	Phase I Trial	DA	R	Phase II/III Trial	DA	R
Substrate Removal	<b>AEB4104, rh Homocystinase</b>	Pre-Clinical: Proof of Concept	Time Lines Unknown							
	Aeglea Biotherapeutics	Initial results presented 2Q17	Time Lines Unknown							
	<b>Erymethionase , Methionine-γ-lyase (MGL)</b>	Pre-Clinical: Proof of Concept	Time Lines Unknown							
	Erytech	Initial results presented 3Q17	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);

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CBS Enzyme Activator	<b>Heme arginate</b>	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					
	<b>Arimoclomol Precursor (Bimoclomol)</b>	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					
	<b>Bortezomib</b>	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					
	<b>SAM Allosteric Activator</b>	Discovery Stage: Target Identification & Validation						
	IM Mendes; University of Lisbon	Targets regulatory domain for CBS	Discovery Status - Time lines cannot be predicted					
	<b>SAM Kinetic Stabilizer of SAM Domain</b>	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						
<b>Cysteamine &amp; mercaptoethylguanidine (MEG)</b>	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	<b>Sulfur amino acids dietary modulation</b>	Pre-Clinical: Proof of Concept						
		Needs validation in clinical trial	Requires funding and sponsor for a clinical trial Time Lines cannot be predicted					
	<b>Cysteine &amp; Taurine Supplements</b>	Pilot Trial completed for CBS						
J.L. van Hove, University of Colorado	Positive effects with abnormal endothelial function	Time Lines Unknown						

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