Paris NASH Meeting

International Think Tank

September 7 & 8, 2023
Institut Pasteur
9th edition

Boehringer Ingelheim
Creating synergies for patients

A holistic approach to Cardio-Renal-Metabolic drug development

Judith Ertle, Germany

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Conflict of interest disclosure

- I am an employee of Boehringer Ingelheim International

Boehringer Ingelheim is a large, global, family-owned company

>53 000 employees worldwide

176 affiliated companies globally

€4.6 billion R&D expenditure*

24.8% of net sales in 2022

We are proud of our heritage in Cardio-Renal-Metabolic diseases and remain committed to prioritizing them as a key focus area

*Data for Human Pharma division.
Boehringer Ingelheim Annual Report, 2022; available at https://annualreport.boehringer-ingelheim.com/2022/downloads/en/BOE_AR22_Financial-Report_EN_safe.pdf; accessed March 2023.

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In our continued commitment of value through innovation, we will leverage our heritage in Cardio-Renal-Metabolic research to address areas of unmet need

Holistic

Considering the broad therapeutic needs of patients with Cardio-Renal-Metabolic conditions connected by similar pathologies

Synergistic

Exploring common Cardio-Renal-Metabolic pathways to identify innovative medicines

Patient-centric

Developing therapies that integrate all aspects of disease management, from behavioural changes to pharmacotherapy

Boehringer Ingelheim. Data on file.

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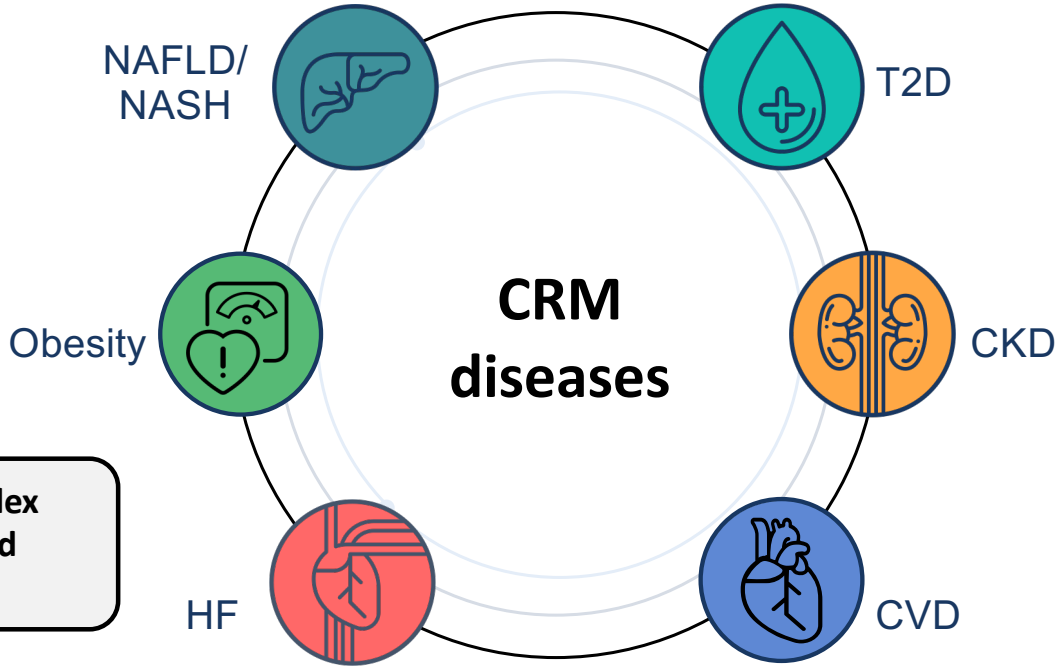
Our current focus areas in Cardio-Renal-Metabolic disease are highly interrelated, meaning improvements in one area can have additional benefits in others[1,2]



CRM diseases are driven by a complex interplay of genetic, biological, and environmental factors[3]

CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2D, type 2 diabetes.

1. Boehringer Ingelheim, 2022. Interconnected CRM conditions; available at https://www.boehringer-ingelheim.com/metabolic-diseases/diabetes/interconnected-crm-conditions; accessed March 2023; 2. Boehringer Ingelheim, 2022. CardioMetabolic disease research and development; available at https://www.Boehringer-ingelheim.com/sites/default/files/Prescription_Medicine/metabolic_diseases/CardioMetabolic_infographic_Update_2021.pdf; accessed March 2023; 3. Ralston, Nugent. Nat Med 2019.

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Cardio-Renal-Metabolic development pipeline

Based on our experience in T2D and cardiovascular diseases, we are developing a portfolio of novel compounds to address the Cardio-Renal-Metabolic conditions with high unmet medical need

Obesity

Targeting dysregulated energy balance

- GCGR/GLP-1R dual agonist
- Undisclosed appetite modulator
- Further undisclosed compounds

Liver disease

(NASH, cirrhosis/portal hypertension)

Targeting steatosis, inflammation, fibrosis, and endothelial dysfunction

- GCGR/GLP-1R dual agonist
- GLP-1R/FGF21R dual agonist
- sGC activator
- Further undisclosed compounds

CKD

Targeting excess aldosterone, endothelial dysfunction, podocyte loss, and reduction in intraglomerular pressure

- sGC activator
- AS inhibitor
- TRPC6i
- Empagliflozin (SGLT2i)*

MI and heart failure

Targeting reperfusion injury and prevention of heart failure

- Empagliflozin (SGLT2i)*
- Further undisclosed compounds

*Approved for treatment of T2D and for symptomatic heart failure with reduced and preserved ejection fraction. Empagliflozin is not approved in CKD or MI.
AS, aldosterone synthase; CKD, chronic kidney disease; CV, cardiovascular; FGF21R, fibroblast growth factor 21 receptor; GCGR, glucagon receptor; GLP-1R, glucagon-like peptide-1 receptor; NASH, non-alcoholic steatohepatitis; sGC, soluble guanylyl cyclase; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; TRPC6i, transient receptor potential channel 6 inhibitor.

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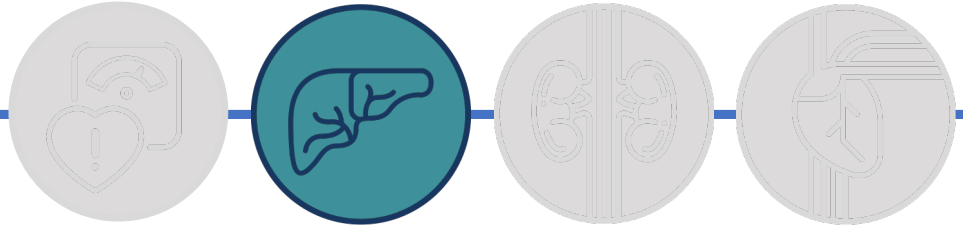
Liver disease

NASH, cirrhosis/portal hypertension



NASH, non-alcoholic steatohepatitis.

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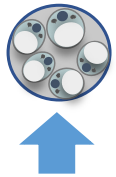
Survodutide (dual GCGR/GLP-1R agonists) may affect the liver through two different pathways, unlike other dual GLP-1-based agonists

GCG/GCGR:[1,2]

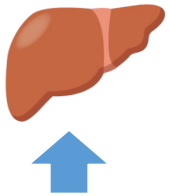
↑ Energy output (metabolic rate)

Adipose tissue (indirect)



Lipolysis

Liver

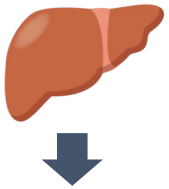


Fatty acid oxidation
Glycogenolysis
Gluconeogenesis
Lipolysis

GLP-1/GLP-1R:[1,2]

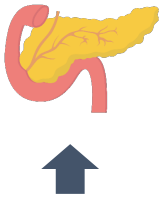
↑ Insulin secretion ↓ Food intake

Liver



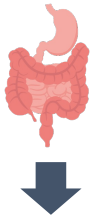
Steatosis

Pancreas



Glucose-dependent insulin secretion

GI tract



Gastric emptying

Brain

Food intake/appetite (hypothalamic centers)

Dual agonism of GCGR and GLP-1R affects the liver through multiple direct and indirect mechanisms, and may offer improvements to people living with NAFL, NASH, and fibrosis[3,4]

GCG, glucagon; GCGR, glucagon receptor; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor.

1. Del Prato et al. Obes Rev 2021; 2. Sánchez-Garrido et al. Diabetologia 2017; 3. Rosenstock et al. ObesityWeek 2022; 4. Boehringer Ingelheim. Data on file.

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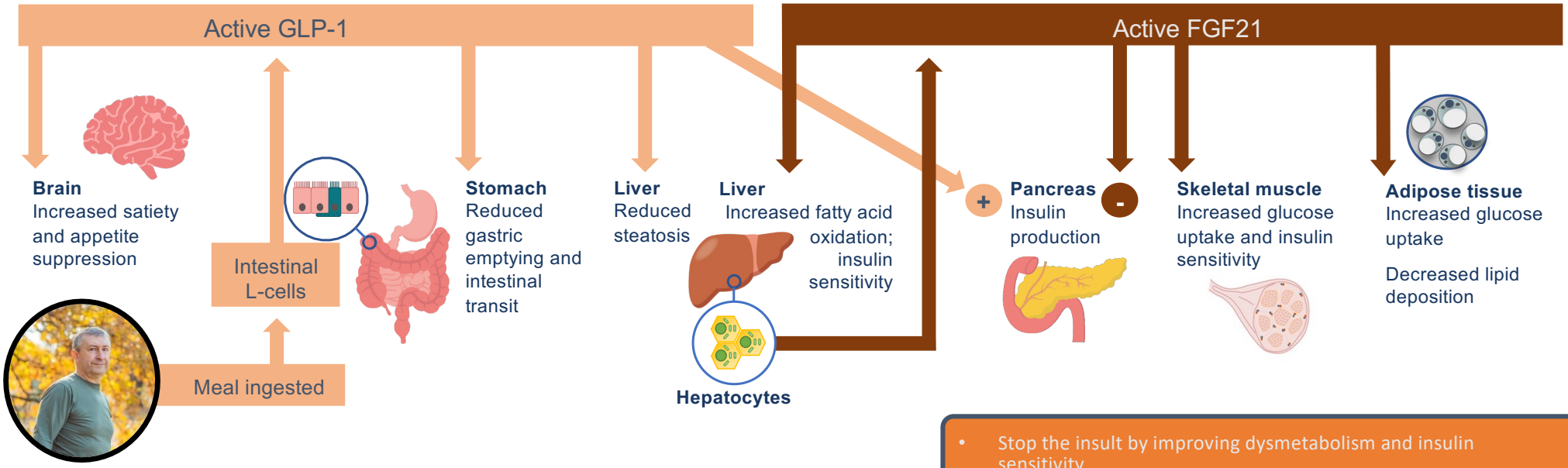
GLP-1R/FGF21R dual agonists have the potential to improve multiple pathological aspects relevant to NASH



- GLP-1: stimulates insulin secretion and regulates appetite
- FGF21: stimulates glucose uptake into adipocytes and skeletal muscle; insulin-sensitizing effect

Possible benefits

- Stop the insult by improving dysmetabolism and insulin sensitivity
- Block effectors by reducing inflammation and fibrosis
- Restore liver function by protecting hepatocytes

FGF21, fibroblast growth factor 21; FGF21R, fibroblast growth factor 21 receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; NASH, non-alcoholic steatohepatitis. Zarei et al. Trends Pharmacol Sci 2020; Tucker et al. Metabolism 2019; Liu et al. EBioMedicine 2019; Sánchez-Garrido et al. Diabetologia 2017; Nakatani et al. Diabetes Metab 2017; Dhir, Cusi. J Investig Med 2018; Camporez et al. Endocrinology 2013.

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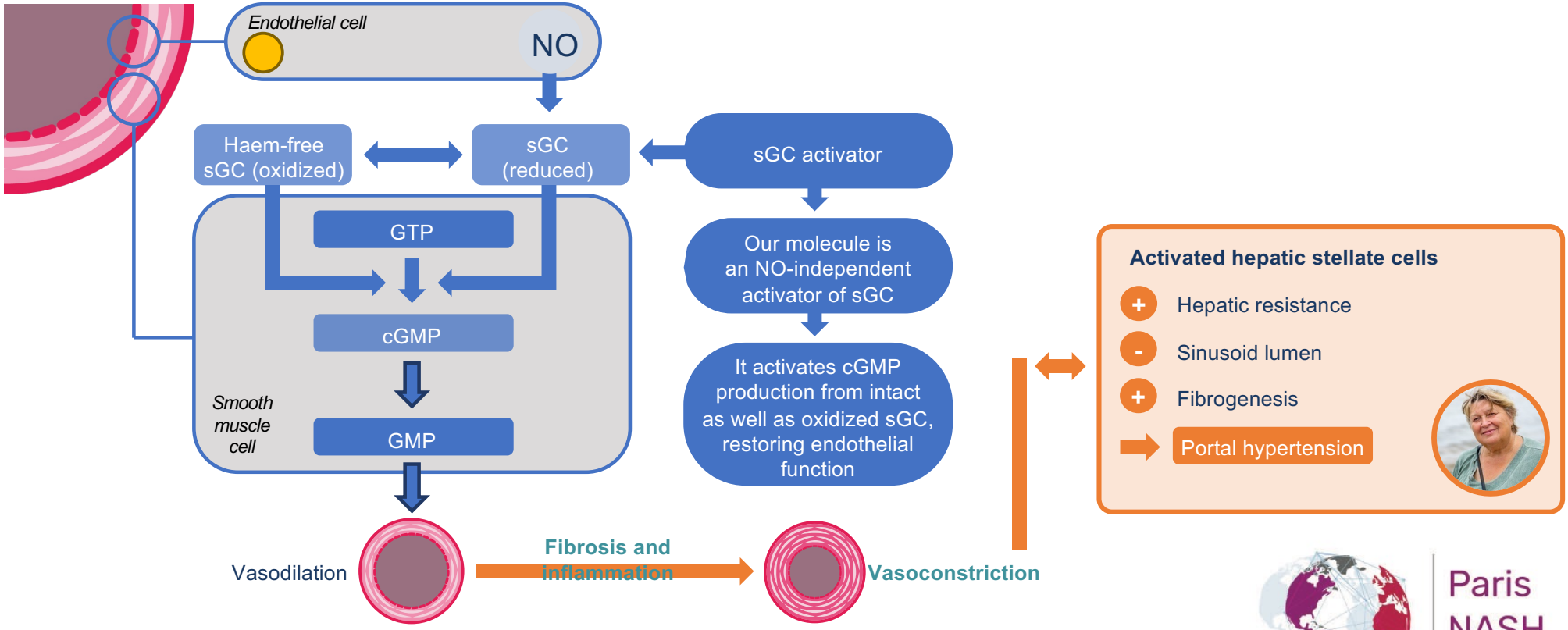
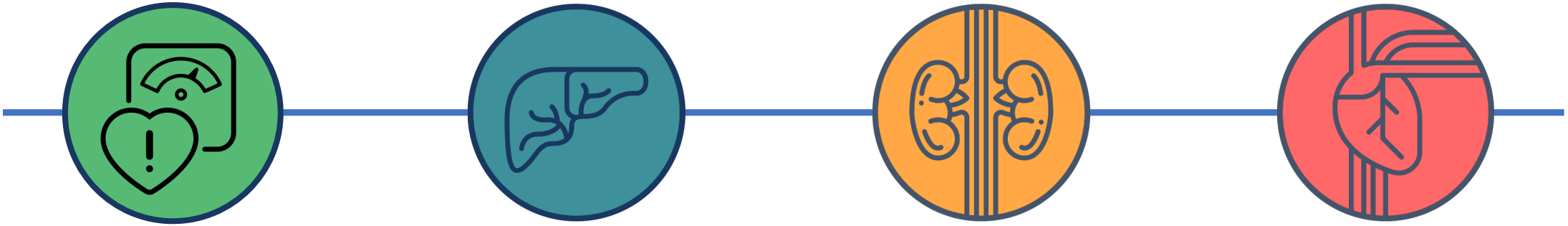
The NO/sGC/cGMP signalling cascade plays an important role in maintaining endothelial function and vasodilation



cGMP, cyclic guanosine monophosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; sGC, soluble guanylyl cyclase.
Lundberg et al. Nat Rev Drug Discov 2015; Rockey. Clin Liver Dis 2006; Krishnan et al. Int J Mol Sci 2018; Stasch et al. Curr Opin Pharmacol 2015.

Thank you!



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