DIREZIONE MEDICA

L’impegno di Novartis nella ricerca cardiovascolare

74° Congresso Nazionale FIMMG-METIS 2017
S. Margherita di Pula (CA)
5 ottobre 2017

Giuseppe Maiocchi
Responsabile Medico Area Cardio-Metabolica

NOVARTIS

Novartis: chi siamo

>54.000 collaboratori

Le nostre terapie raggiungono

un miliardo di pazienti

in

140 Paesi

di tutto il mondo

NOVARTIS

Ricerca e Sviluppo in Italia

- Il contributo dell'Italia all'innovazione si esprime in un forte impegno nella ricerca clinica farmaceutica.
- Per numero e qualità di studi, l'Italia svolge un ruolo significativo nelle strategie della ricerca del Gruppo.

Investimenti Ricerca e Sviluppo
63 milioni di euro

Studi sostenuti
180

Centri ospedalieri
2.514

Pazienti
11.020

NOVARTIS

La ricerca clinica farmaceutica in Italia	STUDI	PAZIENTI	CENTRI
Oncologia ed Ematologia	85	2.121	1.040
Cardiometabolico	18	1.947	422
Immunologia e Dermatologia	39	1.642	334
Neuroscienze	18	1.695	229
Oftalmologia	9	1.426	246
Respiratorio	11	2.189	243
	180	11.020	2.514*

(*) I centri che partecipano a studi in diverse aree terapeutiche sono conteggiati più volte; all'interno di una stessa area terapeutica, il centro è conteggiato una sola volta (anche nel caso partecipi a più studi).

Gli studi clinici: porta dell'innovazione, opportunità e risorsa per il Paese

Posizione dell'Italia per qualità delle pubblicazioni scientifiche a livello internazionale
(media tra documenti citabili, citazioni, H-index)

Nel 2016 le imprese del farmaco hanno investito **700 milioni di euro in studi clinici**, presso le strutture del Ssn

L'Italia ha le caratteristiche per diventare un hub **per gli studi clinici**: vanta solide competenze scientifiche ed eccellenze nell'industria, nelle università e nelle strutture del Ssn

Investire in studi clinici significa non solo **rendere disponibili terapie innovative per i pazienti**, ma anche **assicurare al Ssn importanti risorse e meno costi**, poiché le imprese si fanno carico di tutte le spese ad essi connesse (in oncologia per 1 euro investito, il SSN ne risparmia 2,2)

FARMINDUSTRIA

Fonte: Farmindustria, EY, SciMago, Aifa

Novartis Institutes for BioMedical Research (NIBR)

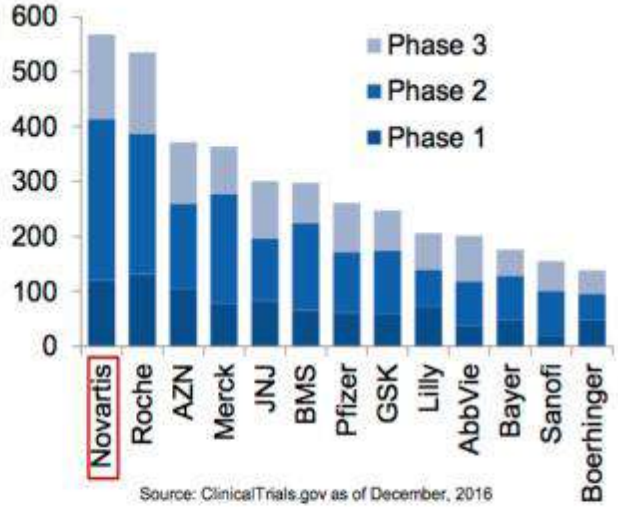
Drug discovery and early development

~6,000

Scientists / 7 sites globally

>500

Ongoing clinical trials (NIBR & GDD)



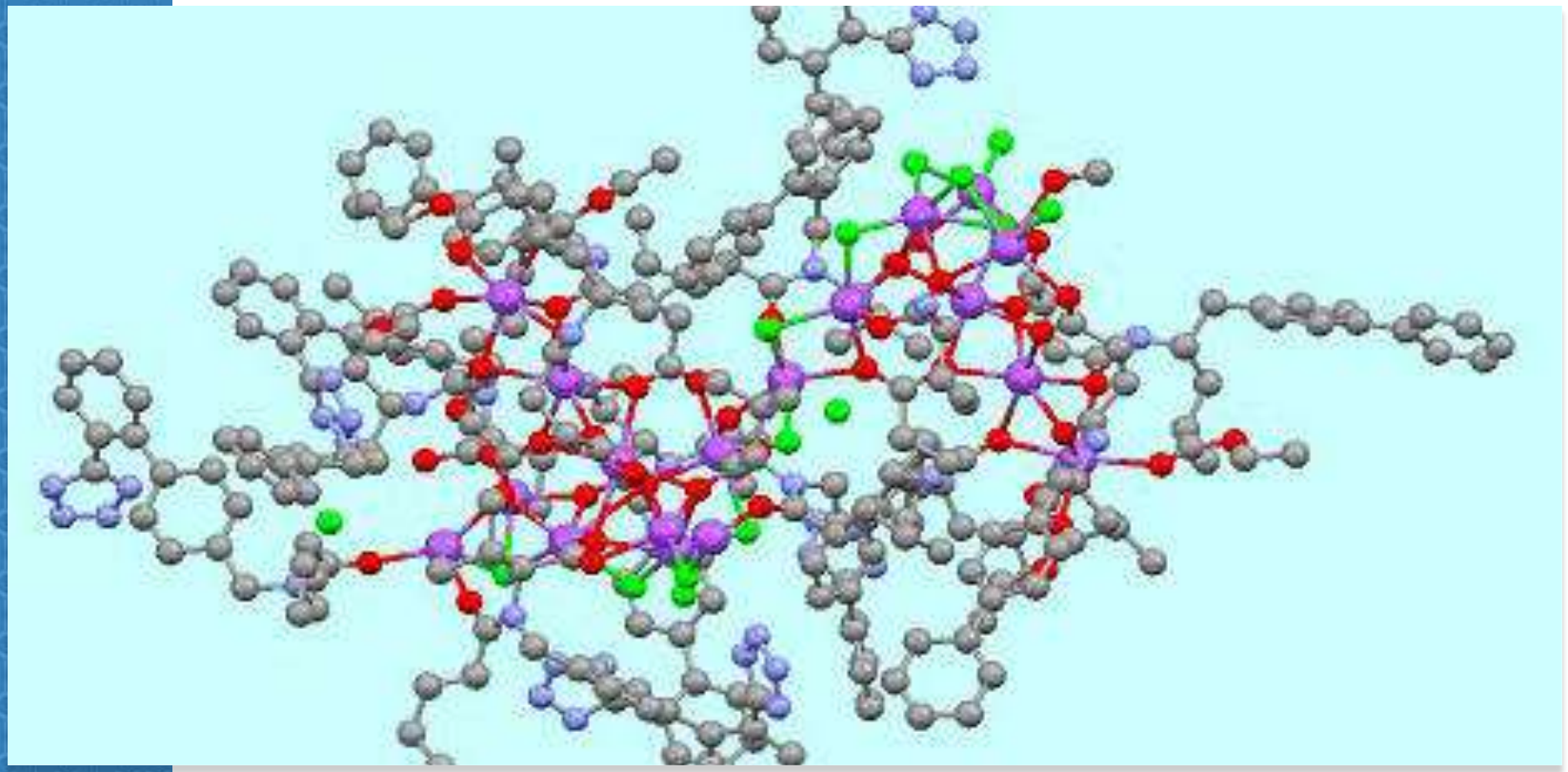
~400

Research projects

~90

New Molecular Entities

NOVARTIS

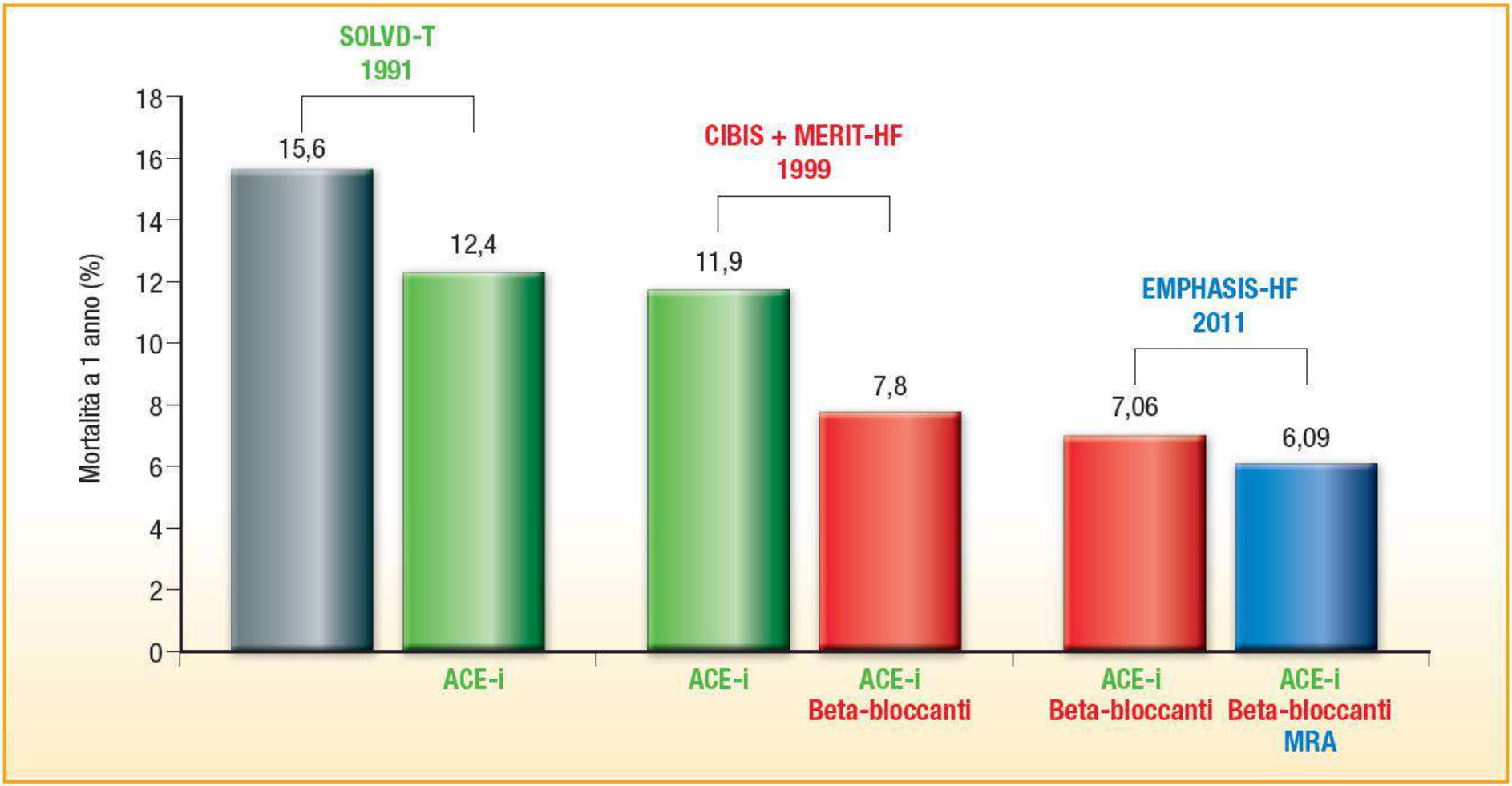


Sacubitril / valsartan:

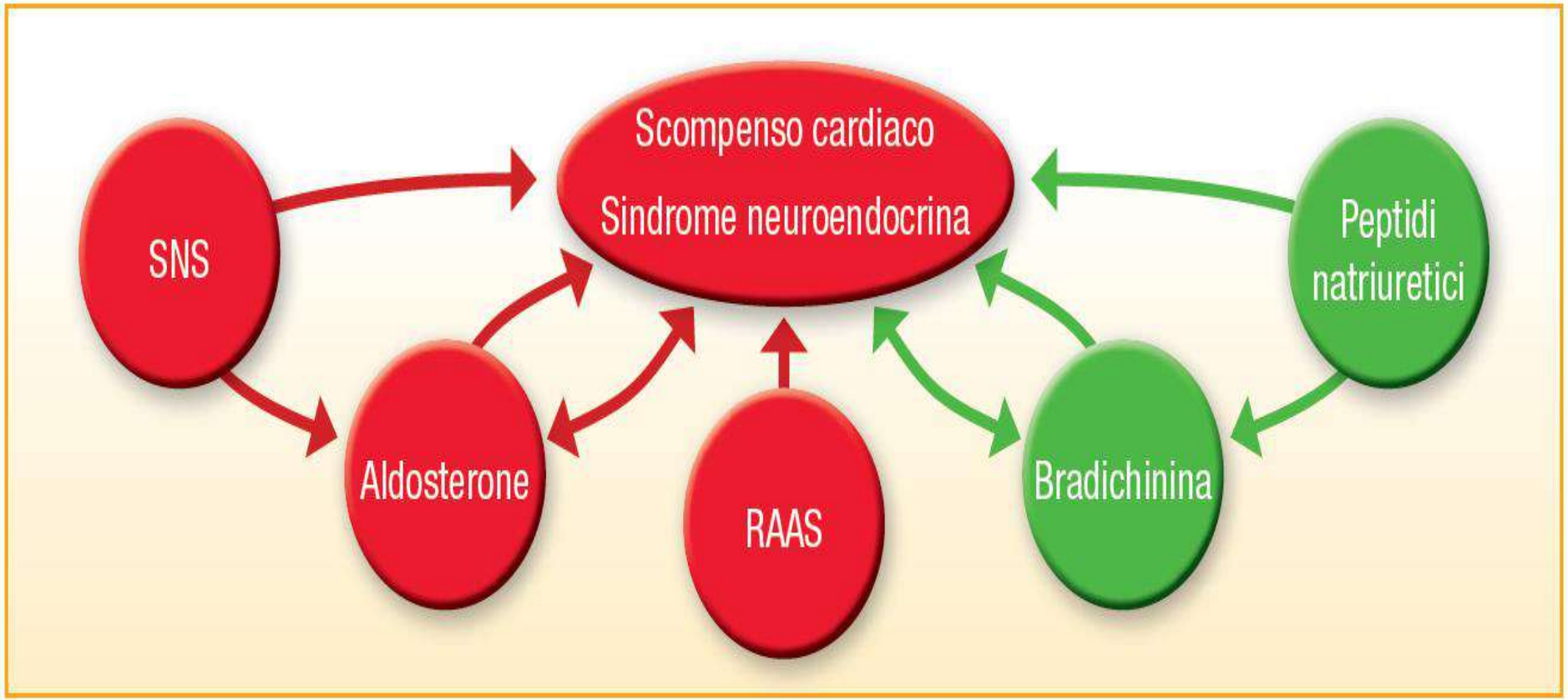
il presente

NOVARTIS

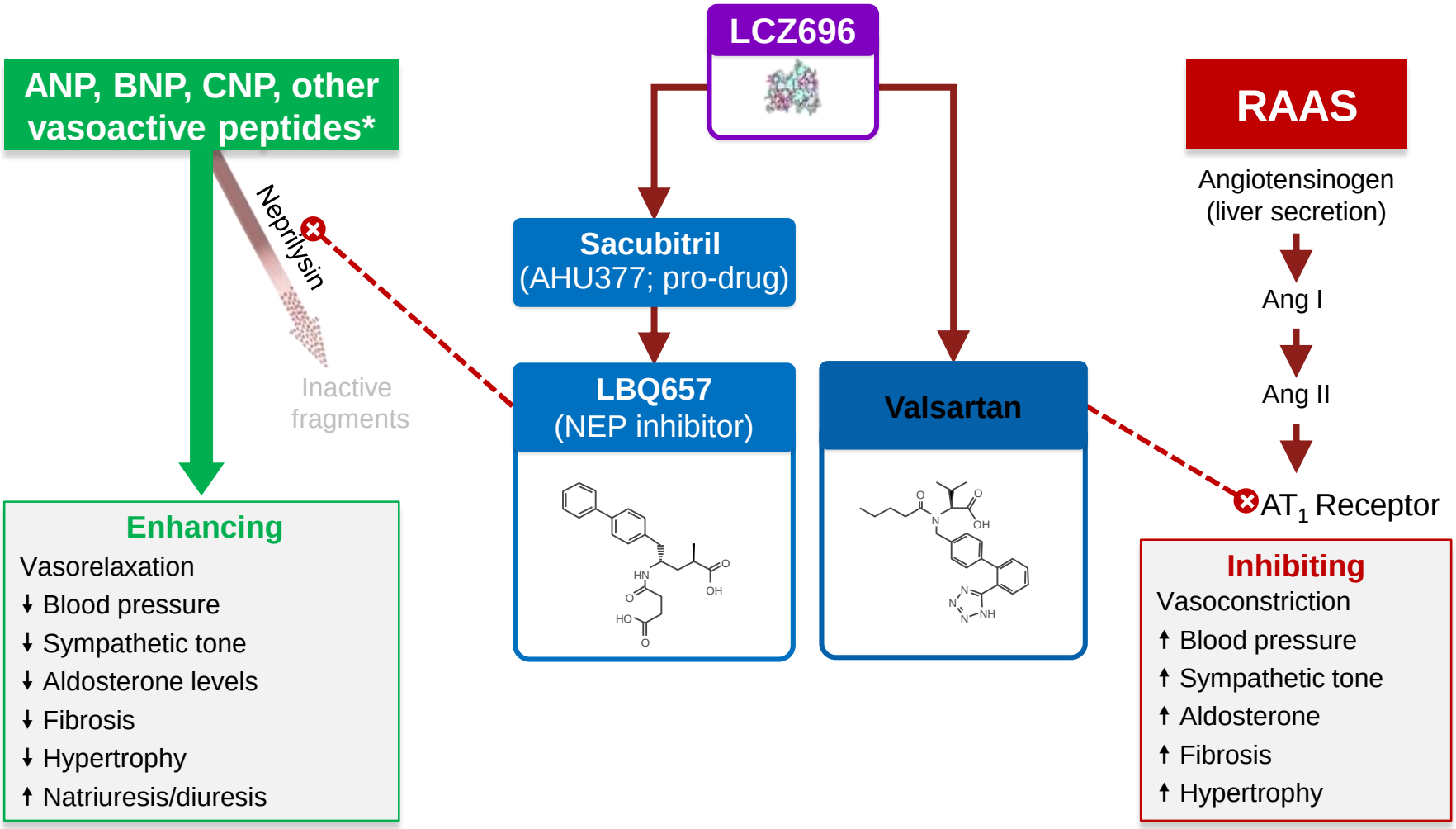
Effetto incrementale della modulazione combinata della sindrome neuro-ormonale



Principali sistemi di regolazione alla base della sindrome neuro-ormonale, con significato prognostico negativo (in rosso) o positivo (in verde)



LCZ696 simultaneously inhibits NEP (via LBQ657) and blocks AT1 receptors (via valsartan)



PARADIGM-HF

Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

McMurray, Packer et al. N Engl J Med 2014; 371(11):993-1004

PARADIGM-HF results

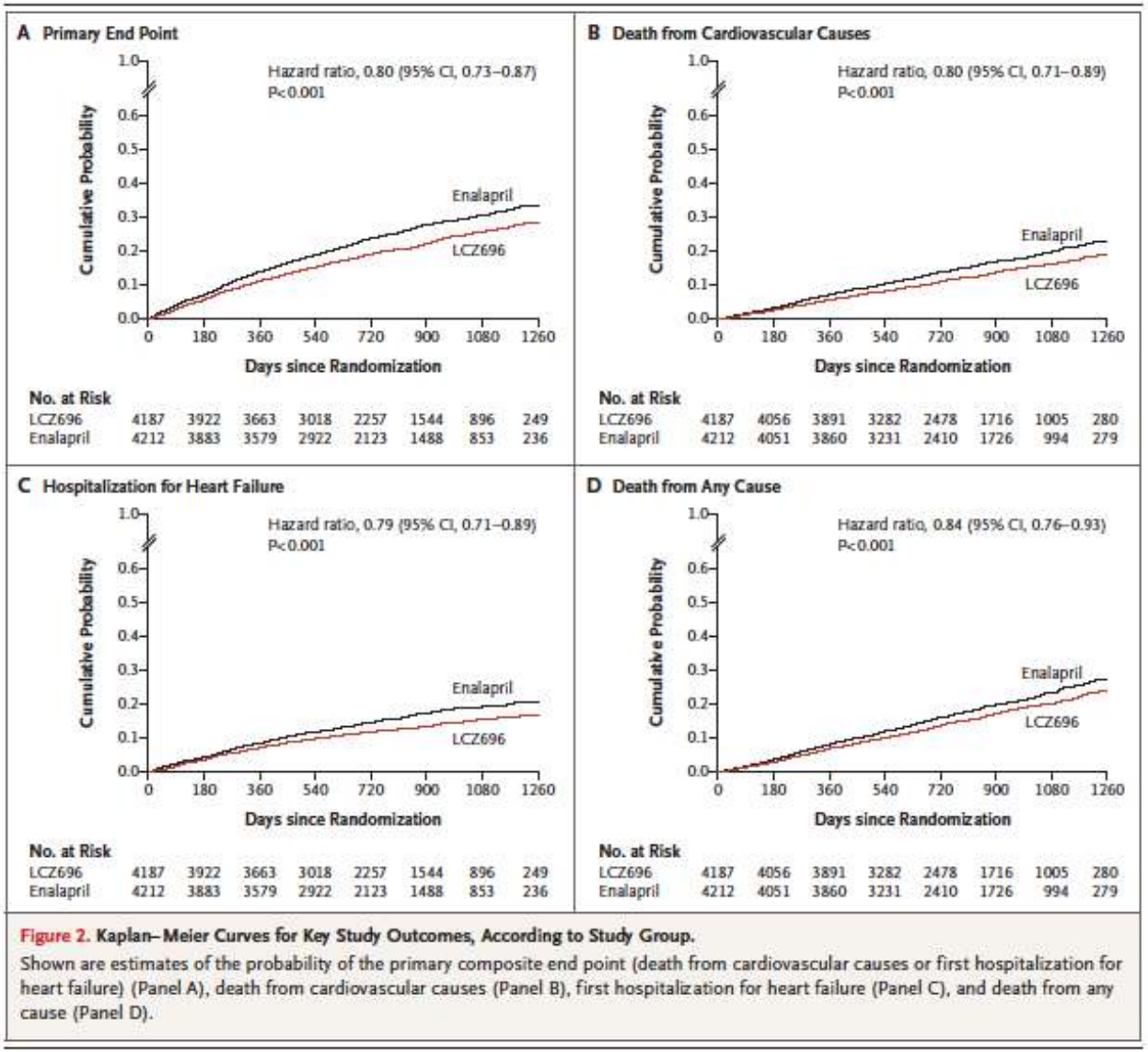


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

N Engl J Med 2014;371:993-1004.

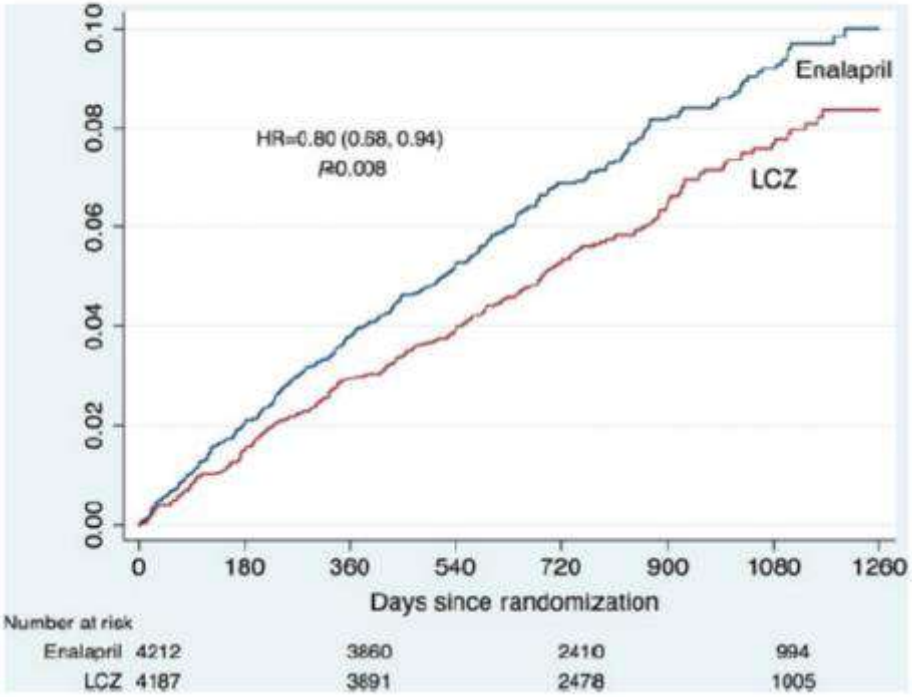
European Heart Journal (2015) **36**, 1990–1997
doi:10.1093/eurheartj/ehv186

CLINICAL RESEARCH
Heart failure/cardiomyopathy

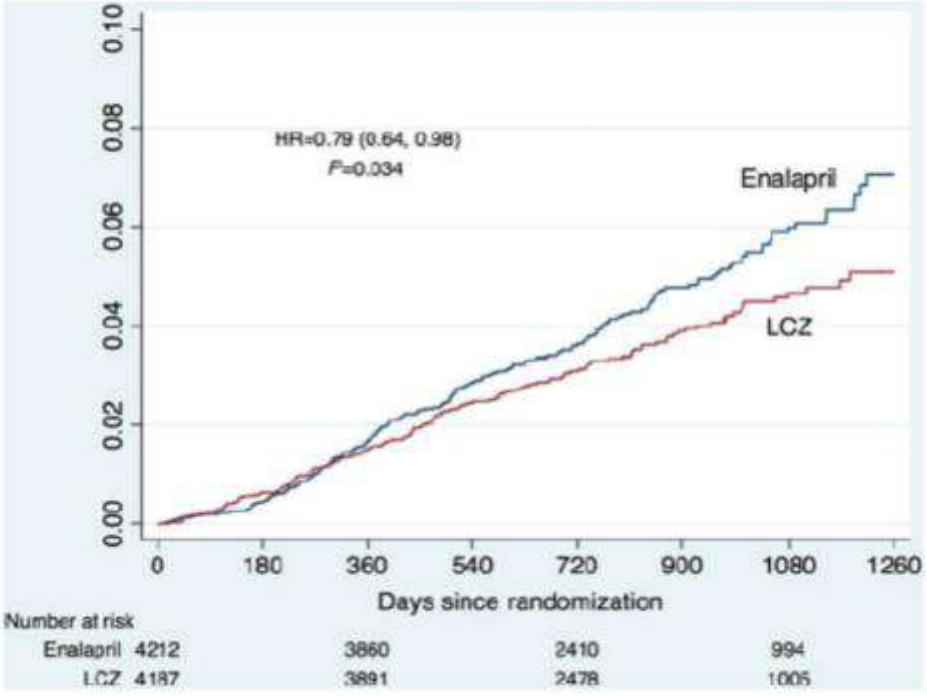
Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients

Akshay S. Desai[1], John J.V. McMurray[2], Milton Packer[3], Karl Swedberg[4,5], Jean L. Rouleau[6], Fabian Chen[7], Jianjian Gong[7], Adel R. Rizkala[7], Abdel Brahimi[1], Brian Claggett[1], Peter V. Finn[1], Loren Howard Hartley[1], Jiankang Liu[1], Martin Lefkowitz[7], Victor Shi[7], Michael R. Zile[8], and Scott D. Solomon[1]*

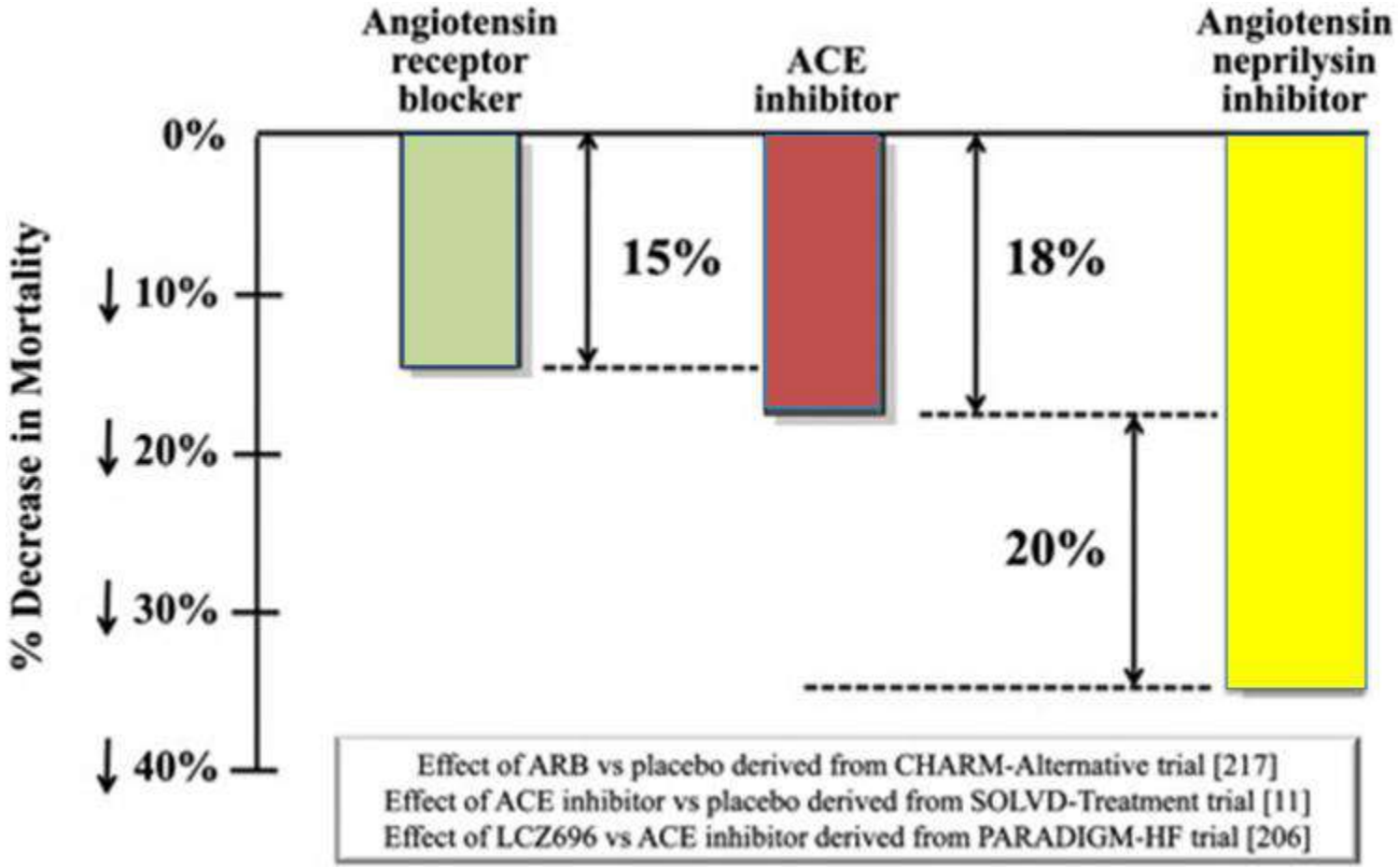
Sudden death



Death due to worsening HF

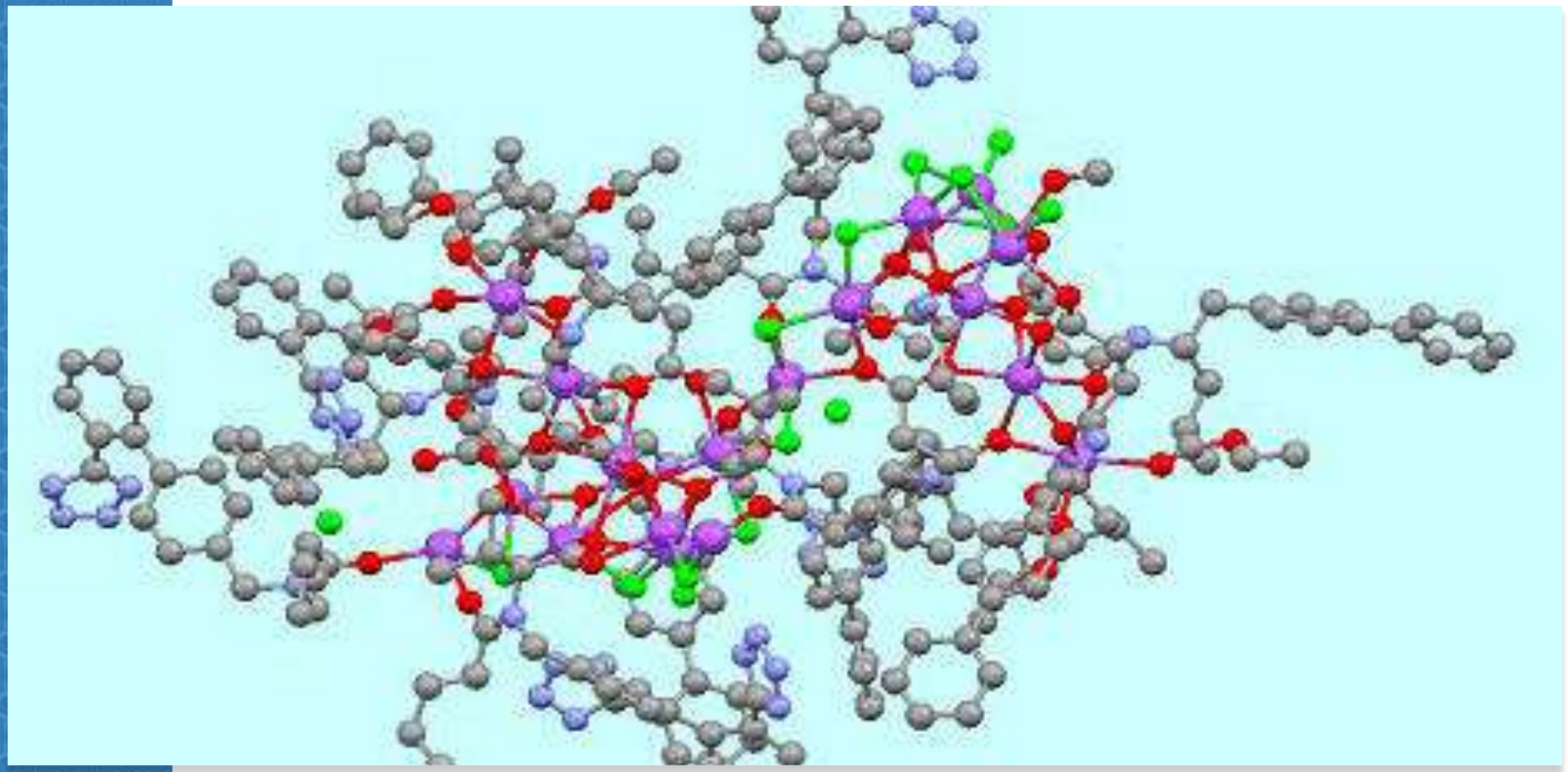


Sacubitril/valsartan raddoppia il beneficio nella riduzione della morbi-mortalità ottenibile con gli ACEi in pazienti HFrEF



Volpe, Carnovali: Clinical Science (2016) 130, 57–77 doi: 10.1042/CS20150469

NOVARTIS



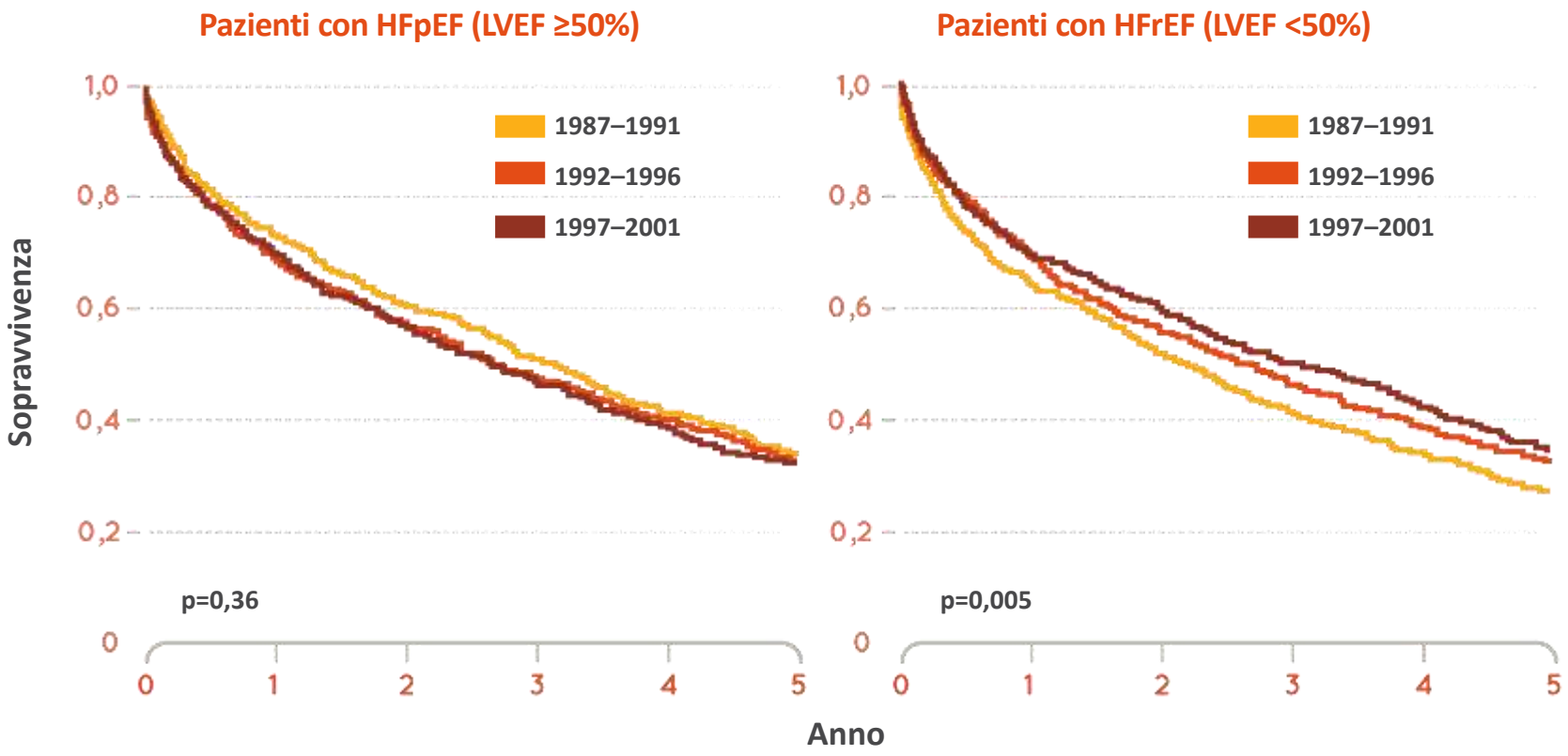
Sacubitril / valsartan:

il futuro… prossimo

NOVARTIS

A differenza dello HFrEF, i tassi di sopravvivenza non sono migliorati nel tempo per lo HFpEF

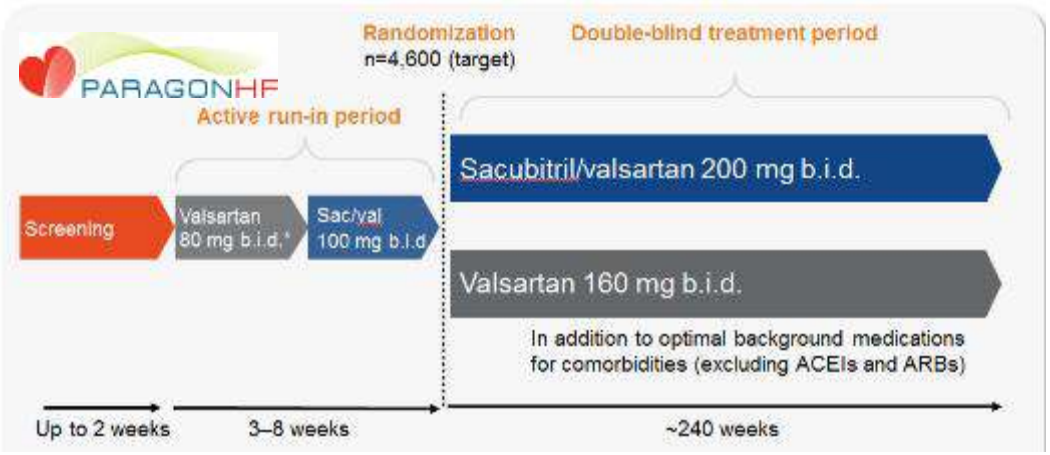
Il tasso di sopravvivenza tra i pazienti con una diagnosi di HFpEF alla dimissione non si è modificato significativamente nel tempo



HFpEF = scompenso cardiaco con frazione d'eiezione preservata; **HFrEF** = scompenso cardiaco con frazione d'eiezione ridotta; **LVEF** = frazione d'eiezione ventricolare sinistra

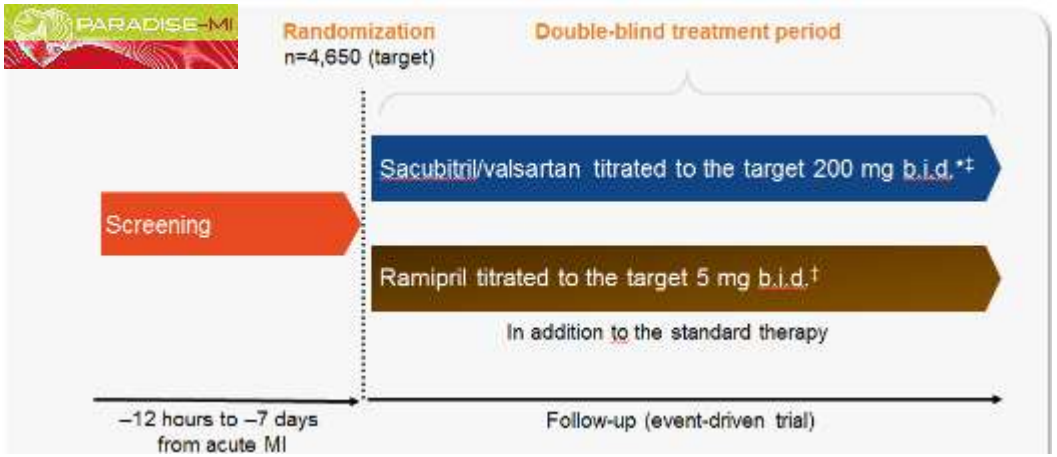
Owan TE et al. N Engl J Med 2006; 355:251–259

PARAGON-HF & PARADISE-MI



Primary objective:
To compare sacubitril/valsartan with valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations

Secondary objectives:
To compare sacubitril/valsartan with valsartan with regard to:
- changes in the clinical summary score for HF symptoms and physical limitations, as assessed by KCCQ scores at 8 months
- improvement in NYHA functional classification at 8 months
- delay in the time to the first occurrence of a composite renal endpoint*
- delay in the time to all-cause mortality



Primary objective:
To demonstrate that sacubitril/valsartan is superior to ramipril in delaying the time to first occurrence of the composite endpoint of CV death, HF hospitalization or outpatient HF

Secondary objectives:
- To compare sacubitril/valsartan with valsartan on:
- delay in time to the first occurrence of CV death or HF hospitalization
- delay in time to new onset of symptomatic HF (time to the first occurrence of HF hospitalization or outpatient HF*)
- delay in time to the first occurrence of CV death, non-fatal spontaneous MI, or non-fatal stroke; reduction in the rates of the composite endpoint of CV death and total (first and recurrent) hospitalizations due to HF, non-fatal spontaneous MI, or non-fatal stroke
- delay in time to all-cause mortality
- safety and tolerability

Sacubitril/valsartan: il futuro… prossimo

Trial	Indication	Status	Next expected milestone
PARAGONHF	HF-pEF[1]	Fully enrolled 4 months ahead of plan	Interim analysis 2018 Filing in 2019
PARADISE-MI	Post-AMI[2]	Enrolling	Completion 2019 Filing in 2020
TRANSITION	Pre- vs. post-discharge following ADHF (HF-rEF)	Enrollment on track	Completion 2018
PIONEERHF	In hospital initiation vs. Enalapril following ADHF[3]	Enrollment on track	Completion 2018

1. HF-pEF: heart failure with preserved ejection fraction 2. AMI: acute myocardial infarction 3. ADHF: acute decompensated heart failure

NOVARTIS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

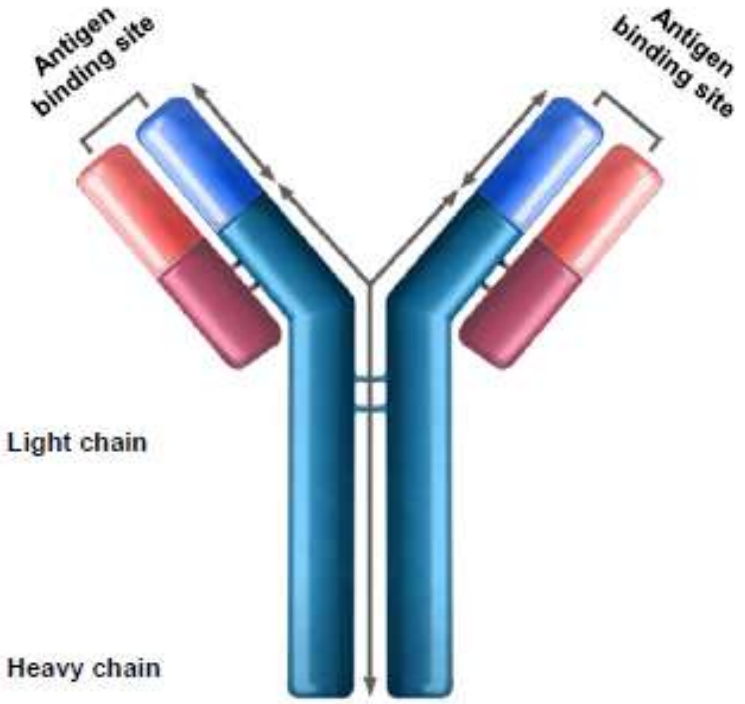
P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

Canakinumab:
Fully human anti-IL-1β monoclonal antibody

- Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody of the IgG1/κ isotype[1]
- Half life: 26 days[2]
- Canakinumab competitively blocks IL-1β binding to both type I and II IL-1 receptors[1]
- Canakinumab is approved for several indications[3]:

  In US and EU:
  - CAPS (Cryopyrin associated periodic syndrome)
  - SJIA (Systemic juvenile idiopathic arthritis)

  In EU:
  - GA (Gouty arthritis)



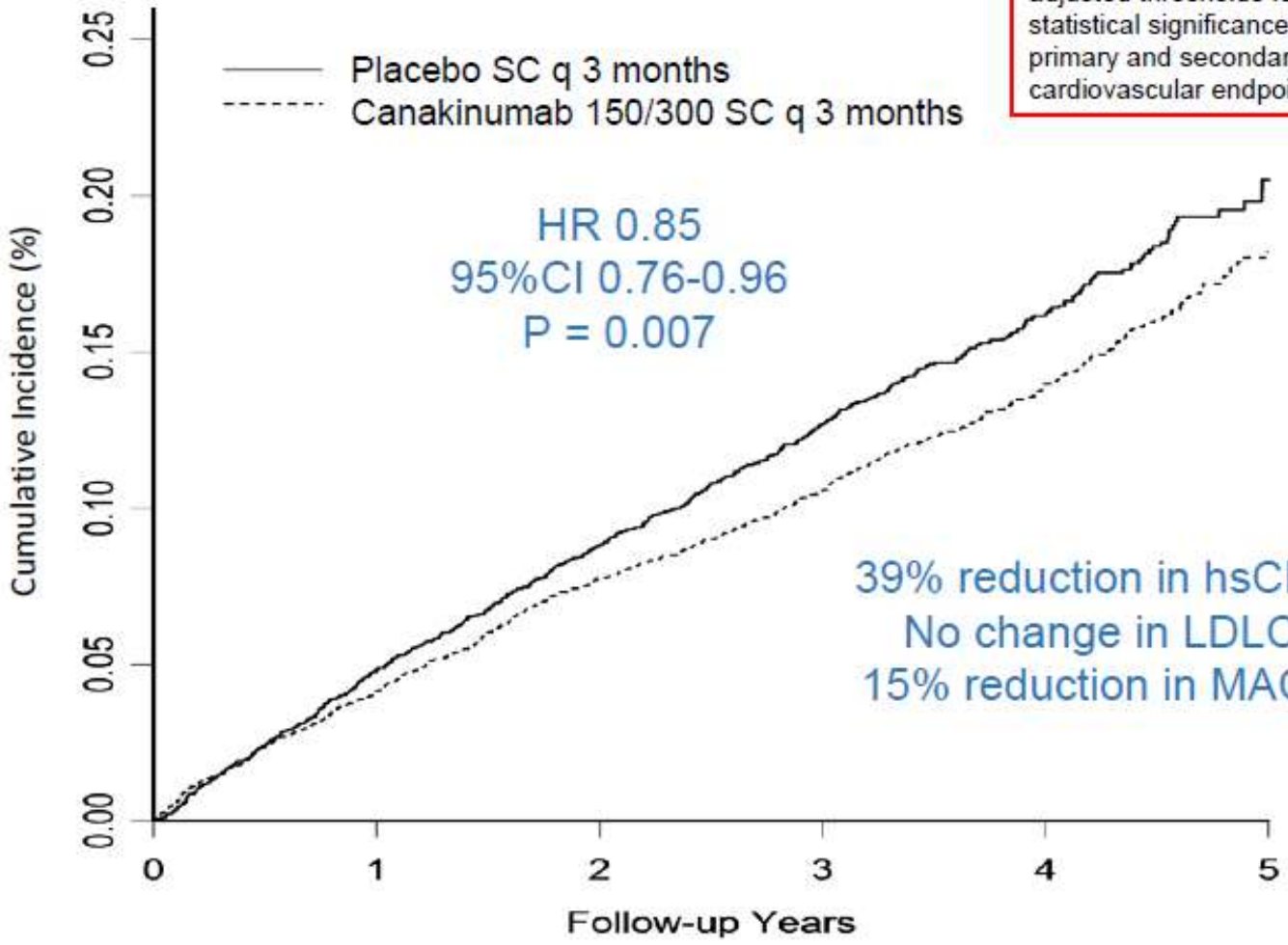
Canakinumab structure[4]

1. Ridker PM, et al. Am Heart J. 2011;162:597-605; 2. Noe A, et al. ClinTher. 2014;36:1625-37
3. European Medicines Agency, 2015: EMA/H/C/001109/P46 041; 4. Chan AC, et al. Nat Rev Immunol. 2010;10:301-16.
CRP, C-reactive protein; IL, interleukin

NOVARTIS PHARMACEUTICALS

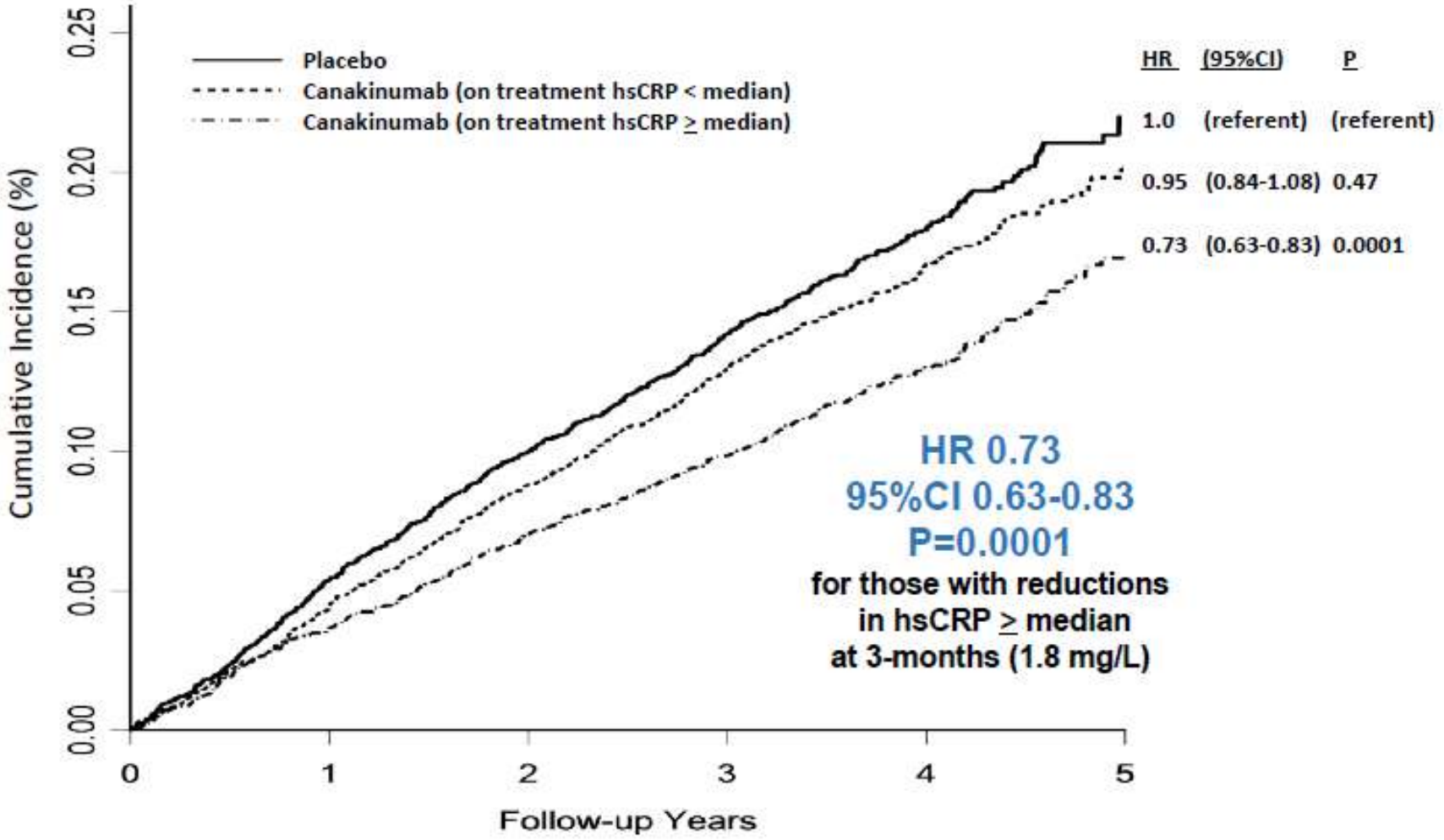
CANTOS: Primary Cardiovascular Endpoint (MACE)

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints



Ridker ESC 2017

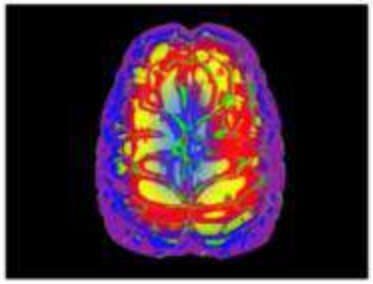
CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)



Ridker ESC 2017

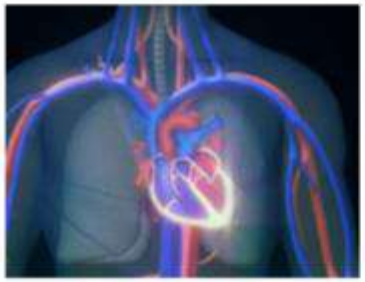
Cardiovascular and Metabolism
Programs in clinical investigation

Stroke Prevention
MAA868: Anti-thrombotic



Weight Loss
LIK066: SGLT1/2 Inhibitor

Resistant Hypertension
LHW090: NEP Inhibitor



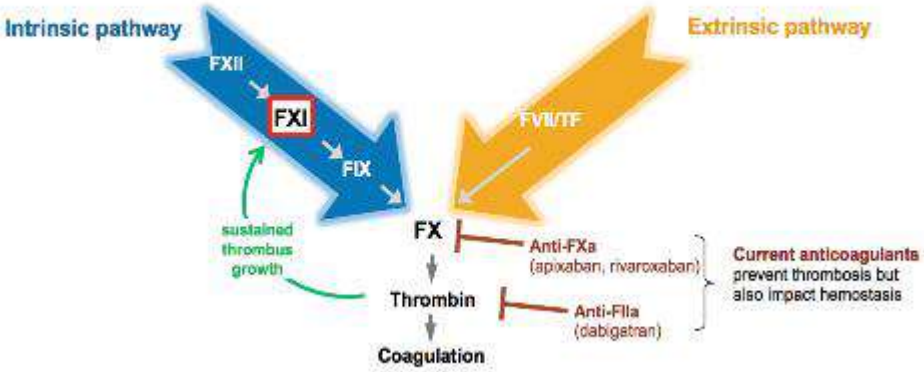
NOVARTIS

MAA868: anti-FXI mAb for treatment of thromboembolic diseases

Exemplary programs in clinical investigation – cardiovascular and metabolism

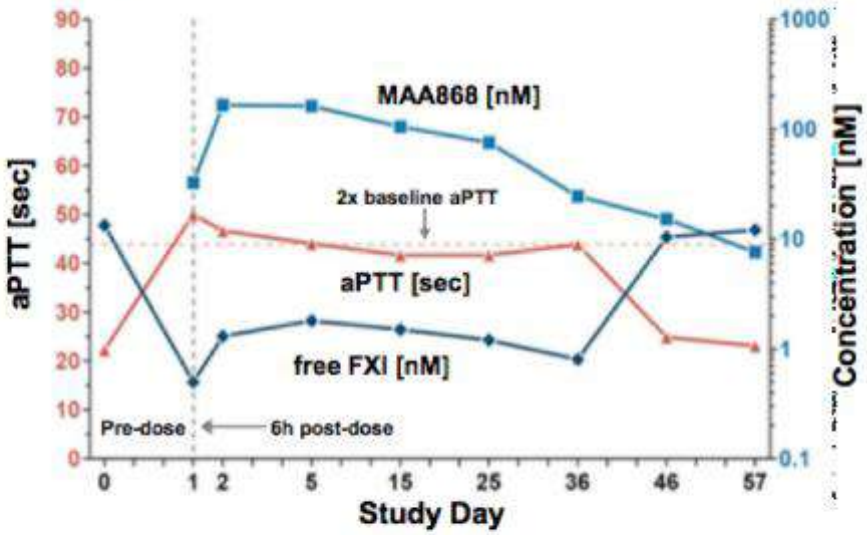
FXI is important for thrombosis but plays a minor role in hemostasis

FXI inhibition has potential of providing efficacy but with a reduced bleeding risk compared to other anticoagulants



MAA868 shows sustained anticoagulant activity in a pre-clinical model

Single subcutaneous dose doubles coagulation time (aPTT ↑ by ~2x) and inversely lowers free FXI for >30 days



Next steps: start of Ph 2b dose range finding study

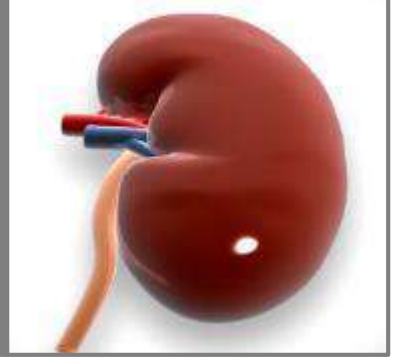
Source: NIBR in-house data. Investigational. Efficacy & safety not yet established CD = catalytic domain.

NOVARTIS

Public info available on internet

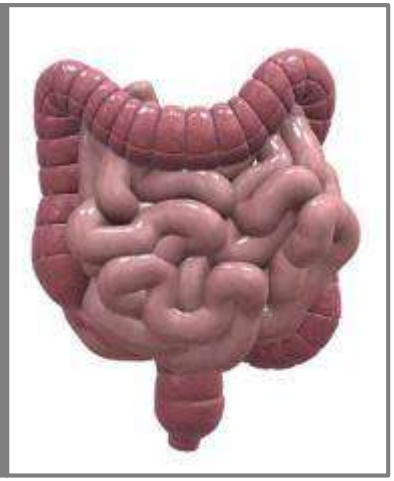
LIK066 improves multiple metabolic parameters & delivers significant weight loss

Kidney



LIK066 blocks reabsorption of filtered glucose by **SGLT1 and SGLT2 in the kidney**, resulting in increased loss of glucose through the urine compared to SGLT2 inhibitors

Intestine

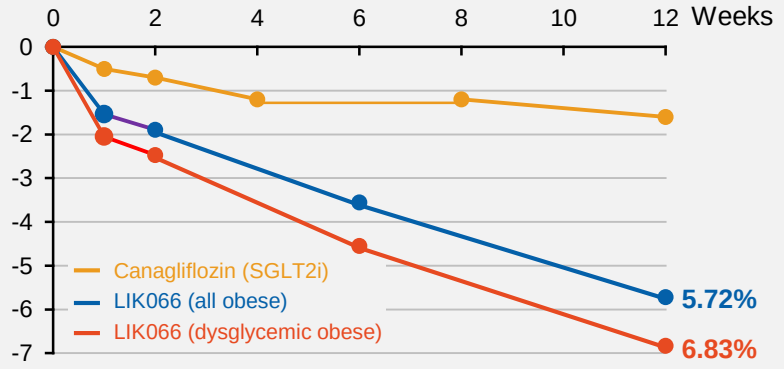


LIK066 inhibits **intestinal SGLT1** which delays/reduces intestinal glucose absorption and stimulates distal L and K cells to release incretin hormones which stimulate insulin secretion and reduce hunger

LIK066 is differentiated versus metabolic and weight loss competitors

- PoC data projected 10-15% PBO-adjusted weight loss at 52 weeks
- Additional expected benefits include improved glycemic control, lipid profile, BP
- Possible reno-protective effects

Change in today body weight
%, placebo corrected

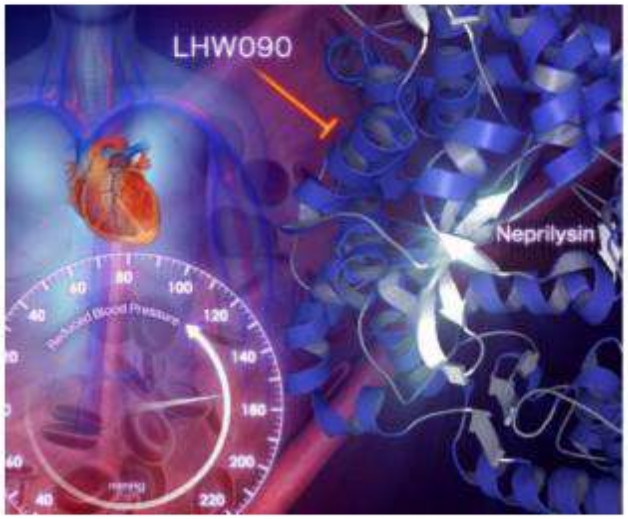


NOVARTIS

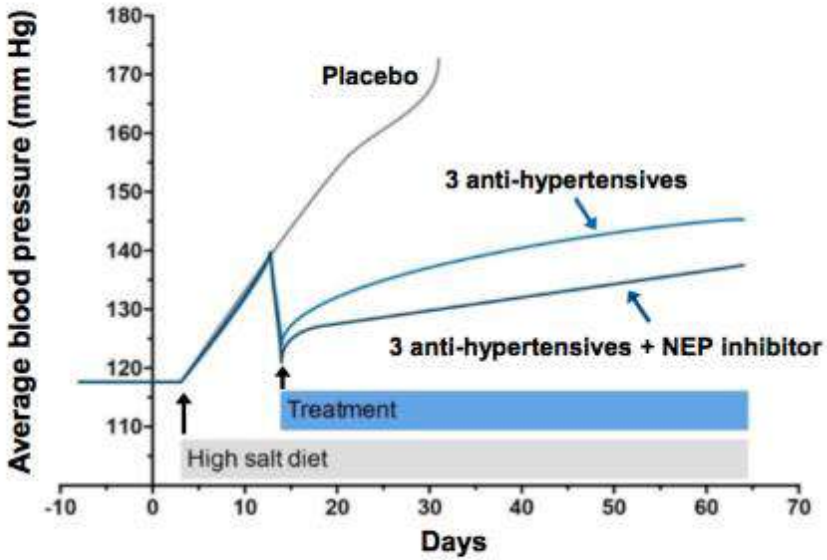
LHW090: neprilysin (NEP) inhibitor for resistant hypertension

Exemplary programs in clinical investigation – cardiovascular and metabolism

Patients with resistant hypertension have blood pressure above goal despite concurrent use of 3 anti-hypertensive agents of different classes, and have a ~ 4-fold increased risk for cardiovascular events[1]



NEP inhibitor attenuated Blood Pressure response when used in combination with 3 drugs in a pre-clinical model



Next steps: start of Ph 2b dose range finding study

Source: NIBR in-house data. Investigational. Efficacy & safety not yet established. [1] Pierdomenico et al., AJH, 2005

NOVARTIS

Public info available on internet

Novartis rende disponibili protocolli e risultati degli studi

European Clinical Trials Database
EudraCT

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Clinical Trial
Results Database

Novartis pubblica sul proprio sito www.novctrd.com le sintesi dei report degli studi clinici

ClinicalStudy
DataRequest.com

I ricercatori possono chiedere l'accesso ai dati dei pazienti, resi anonimi, attraverso un portale pubblico
https://www.clinicalstudydatarequest.com

NOVARTIS

NOVARTIS

Home Clinical trial results

Novartis launched the results website in 2005 becoming one of the first companies to publicly post results from Phase 2b-4 interventional trials. The Novartis position evolved over time to include public disclosure of results from Phase 1- 2a interventional trials in patients.

Drug development process

Drug development begins and ends with the patient.

READ MORE

Transparency position

Novartis is committed to the timely registration of trials and posting of results.

READ MORE

Clinical trial results

Clinical trials are fundamental to the development of innovative products.

READ MORE

ClinicalTrials.gov

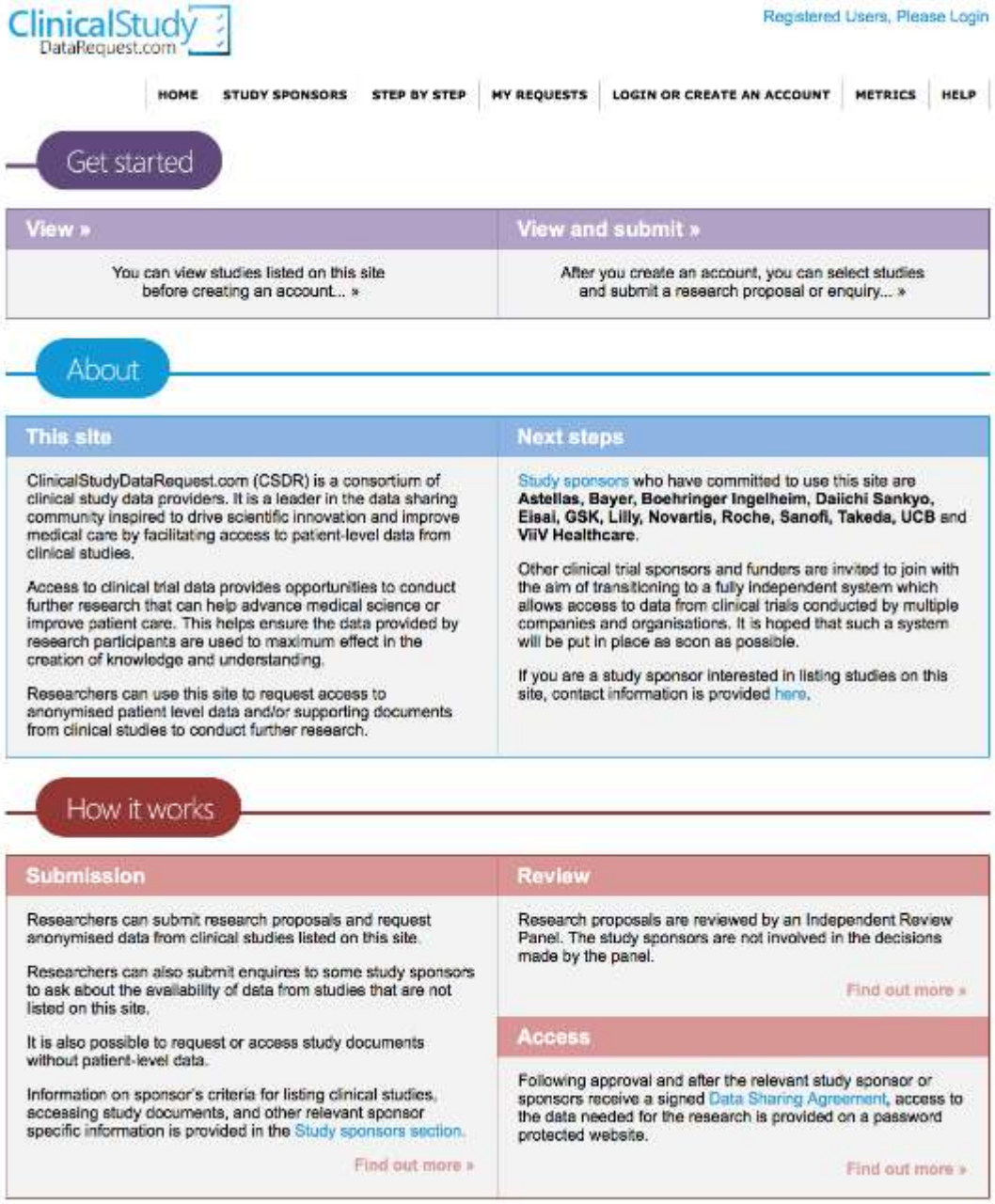
Clinicaltrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

READ MORE

EU clinical trial registry

The EU Clinical trials register contains information on interventional clinical trials on medicines conducted in the European Union (EU).

READ MORE


ClinicalStudy DataRequest.com
Registered Users, Please Login
HOME
STUDY SPONSORS
STEP BY STEP
MY REQUESTS
LOGIN OR CREATE AN ACCOUNT
METRICS
HELP
Get started
View »
You can view studies listed on this site before creating an account... »
View and submit »
After you create an account, you can select studies and submit a research proposal or enquiry... »
About
This site
ClinicalStudyDataRequest.com (CSDR) is a consortium of clinical study data providers. It is a leader in the data sharing community inspired to drive scientific innovation and improve medical care by facilitating access to patient-level data from clinical studies.
Access to clinical trial data provides opportunities to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by research participants are used to maximum effect in the creation of knowledge and understanding.
Researchers can use this site to request access to anonymised patient level data and/or supporting documents from clinical studies to conduct further research.
Next steps
Study sponsors who have committed to use this site are Astellas, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eisai, GSK, Lilly, Novartis, Roche, Sanofi, Takeda, UCB and ViiV Healthcare.
Other clinical trial sponsors and funders are invited to join with the aim of transitioning to a fully independent system which allows access to data from clinical trials conducted by multiple companies and organisations. It is hoped that such a system will be put in place as soon as possible.
If you are a study sponsor interested in listing studies on this site, contact information is provided here.
How it works
Submission
Researchers can submit research proposals and request anonymised data from clinical studies listed on this site.
Researchers can also submit enquires to some study sponsors to ask about the availability of data from studies that are not listed on this site.
It is also possible to request or access study documents without patient-level data.
Information on sponsor's criteria for listing clinical studies, accessing study documents, and other relevant sponsor specific information is provided in the Study sponsors section.
Find out more »
Review
Research proposals are reviewed by an Independent Review Panel. The study sponsors are not involved in the decisions made by the panel.
Find out more »
Access
Following approval and after the relevant study sponsor or sponsors receive a signed Data Sharing Agreement, access to the data needed for the research is provided on a password protected website.
Find out more »

NOVARTIS