



Agenzia Italiana del Farmaco

AIFA

Workshop on

HEART FAILURE

Rome, November 24-25, 2013

In collaboration with:

European Medicines Agency (EMA)



**HEART FAILURE
ASSOCIATION
OF THE ESC**

Heart Failure Association (HFA)

**FONDAZIONE
GIOVANNI LORENZINI
MILAN, ITALY**



**GIOVANNI LORENZINI
MEDICAL FOUNDATION
HOUSTON, TX, USA**

Sunday, November 24

Hotel delle Nazioni - Campigli Room

17.00

Welcome by the Giovanni Lorenzini Medical Foundation

Introduction to the Meeting

Guido Rasi (UK), **Luca Pani** (I), **Sergio Pecorelli** (I)

Unmet needs: what can be done? The point of view of the regulatory agencies

Giuseppe Rosano (I)

Purpose and goals of the next day's session

Q & A and Discussion

All Participants

19.00

Closing of the session

Monday, November 25

AIFA - Room 2-3-4

8.30 - 8.40

Registration

Chair: Luca Pani (I)

8.45 - 9.00

Luca Pani (I), **Guido Rasi** (UK)

Introductory remarks

9.00 - 9.25

Stefan D. Anker (G)

Heart failure today: where we are, where we should be

9.25 - 9.45

Q & A and Discussion

All Participants

UNMET NEEDS, OPPORTUNITIES

Chair: Andrew Coats (UK and Australia)

- 9.50 - 10.00 **Claudio Ceconi (I)**
Biomarkers in heart failure: limits and opportunities
- 10.00 - 10.10 **Krishna Prasad (UK)**
What do regulators expect from HF trials and how guidelines can help
- 10.10 - 10.20 **Ameet Nathwani (CH)**
The challenges of developing drugs in AHF: an industry perspective
- 10.20 -10.30 **Stefan D. Anker (G)**
The need for better endpoints: the clinicians' view
- 10.30 -10.40 **Paolo D. Siviero (I)**
Reimbursement policies in Europe: values and limits
- 10.40 - 11.10 *Break*
- 11.10 -11.20 **Andrew J. Stewart Coats (UK and Australia)**
Summary of the unmet needs and opportunities presented
- 11.20 - 13.00 **Q & A and Discussion**
Chairs: Marco Metra (I) and Paolo D. Siviero (I)
- All participants
Mitja Lainscak (SLO)
Claudio Mori (CH)
- 13.00 - 14.00 *Lunch*

THE WAY FORWARD

Chairs: Mihai Gheorghide (USA), Mitja Lainscak (SLO)

- 14.00-14.10 **Mihai Gheorghide** (USA)
How to better harmonize clinical needs, innovative trials/methods
- 14.10-14.20 **Andrew J. Stewart Coats** (UK and Australia)
Clinical view of solutions: how to effectively resolve these perceived conflicts
- 14.20-14.30 **Giuseppe Rosano** (I)
Regulatory endpoints
- 14.30-14.40 **Nancy Cook- Bruns** (G)
What are the expectations of the industry?
- 14.40-14.50 **Laura Fregonese** (UK)
Biomarker qualification programs
- 14.50 -15.00 **Americo Cicchetti** (I)
What will be worth paying for
- 15.00-15.10 **Mihai Gheorghide** (USA) and **Mitja Lainscak** (SLO)
Summary of the presented perspectives
- 15.10 - 16.15 **Q & A and Discussion**
Chairs: Stefan D. Anker (G) and Krishna Prasad (UK)

All participants
- 16.15-16.30 **Sergio Pecorelli** (I)
Closing remarks

List of the Participants

Stefan D. Anker - Professor of Cardiology & Cachexia Research - Applied Cachexia Research, Department of Cardiology - Charité, Campus Virchow-Klinikum - Berlin (Germany) - President, Heart Failure Association

Paola Castellani - Head of Clinical Development - Medical Affairs and Patient Advocacy - Region Europe - Novartis Pharma AG - Basel (Switzerland)

Claudio Ceconi - Department of Medical Sciences - Division of Cardiology - University of Ferrara - Ferrara (Italy)

Americo Cicchetti - Director Graduate School of Health - Economics and Management - Catholic University of Sacred Heart - Rome (Italy)

Alessandro Cirrincione - Pricing and Market Access - Global Director - Vifor Pharma - Glattbrugg (Switzerland)

Andrew J Stewart Coats - Academic Vice-President, Monash University, Australia and University of Warwick, UK - Director of the Monash Warwick Alliance - Warwick (UK) and Melbourne (Australia)

Nancy Cook-Bruns - Head Cardiovascular Group - Global Clinical Development - Bayer Pharma Aktiengesellschaft - Elberfeld (Germany)

Emanuela Folco - Secretary General & CEO - Fondazione Giovanni Lorenzini Medical Science Foundation - Milan (Italy) and Houston (USA)

Laura Fregonese - Scientific Administrator - European Medicines Agency (EMA) - London (UK)

Mihai Gheorghiane - Professor of Medicine and Surgery - Director of Experimental Therapeutics - Center for Cardiovascular Innovation Northwestern University Feinberg - School of Medicine - Chicago (USA)

Roland Gordon-Beresford - Sr Director Regulatory Affairs and Intellectual Property - Cardio3 BioSciences S.A. - Mont-Saint-Guibert (Belgium)

Mitja Lainscak - Associate Professor of Internal Medicine - University Clinic Golnik - Division of Cardiology - Golnik (Slovenia) - Heart Failure Association, Patient Care Committee

Guy Lerebours - Medical and Scientific Director - Cardiovascular Research and Development – Servier - Neuilly-sur-Seine (France)

Susan Longman - Head Drug Regulatory Affairs Europe and Greater China - Novartis Pharma AG - Basel (Switzerland)

Patricia Maillere - Director Worldwide Regulatory Affairs - Servier - Neuilly-sur-Seine (France)

Marco Metra - Department of Medical and Surgical Specialities - Radiological Sciences and Public - University of Brescia -Brescia (Italy)

Markus Meyer - Cardiorentis Ltd - Steinhausen (Switzerland)

Claudio Mori - Medical Affairs TA Cardio&New Indication - Medical Lead MA Studies - Vifor Pharma - Glattbrugg (Switzerland)

Ameet Nathwani - Franchise Head Critical Care - Novartis Pharma AG - Basel (Switzerland)

Luca Pani - Director General - Italian Medicines Agency (AIFA) - Rome (Italy)

Sergio Pecorelli - President - Italian Medicines Agency (AIFA) - Rome (Italy)

Andrea Peracino - Vice President - Fondazione Giovanni Lorenzini Medical Science Foundation - Milan (Italy) *and* Houston (USA)

Krishna Prasad - Medicines and Healthcare Products - European Medicines Agency (EMA) - London (UK)

Guido Rasi - Executive Director - European Medicines Agency (EMA) - London (UK)

Giuseppe Rosano - Department of Medical Sciences - IRCCS San Raffaele - Rome (Italy)

Olga Santiago - Executive Global Program Head - Heart Failure - Novartis Pharmaceutical Corporation - East Hanover (USA)

Paolo D. Siviero - Head, Economic Strategy and Pharmaceutical Policy - Italian Medicines Agency (AIFA) - Rome (Italy)

Mary Lou Wratten - Medical Director - Thermo Fisher (B.R.A.H.M.S Italia) - Milan (Italy)

Workshop on Heart Failure

Unmet needs, opportunities, and the way forward

Rome, November 24-25, 2013

HIGHLIGHTS OF THE MEETING

Epidemiology

<i>Some issues from the Workshop</i>	<i>Questions/Challenges</i>	<i>What about tomorrow</i>
<p>Heart failure is a major health crisis. It affects 26 million people worldwide, with an estimate of 6.5 million people in Europe and 6.5 million people in the United States. In each region, 1 million patients are hospitalized every year. Approximately 50% of patients die within 4 years of diagnosis.</p> <p>Heart failure is not a single disease but a final common pathway of many different pathologies, the most common of which is ischemic heart disease in the western world.</p> <p>Heart failure is no longer considered a single entity but rather as different cardiac and noncardiac conditions culminating into a common pathway.</p>	<p>What are the precise figures of mortality, costs and treatment approaches in each European country?</p> <p>What are the reasons for variance?</p> <p>What is the economic burden of the direct and indirect costs in Europe for HF?</p> <p>What is the definition of payer policies in the management of patients with HF in Europe?</p> <p>What is lacking in today's knowledge: Better identification of individual phenotypes?</p> <p>What needs to be considered for therapeutic approaches to HF?</p> <p>What are the definitions of economic costs within each European country?</p>	<p>In the USA, the prevalence of HF in 2010 was 2.8% and this is projected to grow to 3.3% in 2030. Relevant direct costs were \$24.7 billion in 2010, \$31 billion in 2012 and an estimate of \$70 billion in 2030. Indirect costs vary from \$9.7 to \$17.4 million.</p> <p>What is the projection for each European country?</p> <p>What could (or should) be the return on investment for patient treatment at home or in hospital in the next years for every country?</p>

Clinical approach

<i>Some issues from the Workshop</i>	<i>Questions/Challenges</i>	<i>What about tomorrow</i>
<p>“Heart Failure is not a disease and we should no longer approve drugs for a heterogeneous broad population, but for a well defined sub-population where we can demonstrate a marked benefit” (<i>Stephen Grant, Deputy Director, Division of Cardiovascular Renal Products, CDER</i>).</p> <p>Relevant co-morbidities in CHF that require medical attention: CAD / ischemia Hypertension, Diabetes mellitus. Depression / other neurological disease, Renal dysfunction and kidney injury, Anemia and iron deficiency, COPD, Liver & bowel dysfunction, Cachexia.</p> <p>Develop agreements on specific patient populations.</p> <p>Worsening of Heart Failure: meaningful change in clinical status leading to intensification of therapy; the following change in therapy may confound identification and interpretation of any treatment effect.</p> <p>Basic researchers will continue to unravel the complexity of HF and identify mechanisms of disease that lead to final common pathways of heart failure.</p>	<p>Joint activity of HFA with EMA and AIFA and particular scientific trust in new pathways of approval, longer commercialization and new prices and reimbursements.</p> <p>It is recommend that patients with heart failure are enrolled in a multidisciplinary-care management program to reduce the risk of heart failure hospitalization. It is recommended that regular exercise is encouraged in patients with heart failure to improve functional capacity and symptoms. Patients suffering with acute heart failure should be treated as early as possible.</p> <p>Which endpoint, beyond mortality and dyspnea, should be the final aim?</p> <p>Should the industry continue to invest in drugs for heart failure when no drug has been approved in the last 15 years?</p> <p>Many drugs are likely to require a trial, which includes survival amongst its primary objectives before requesting an approval regardless of the claim being sought.</p> <p>Reimbursement value of CV drugs is too low compared to cancer, HIV, hepatitis.</p> <p>Need to identify and define clinical entities besides acute and chronic heart failure.</p> <p>Definition of clinically meaningful end points that may also be of importance for payers.</p> <p>Specific <i>concerns</i> and potential solutions related to patients hospitalized with Heart Failure.</p>	<p>The need for smarter trials.</p> <p>Use adaptive trial designs (or adaptive licensing).</p> <p>Use simplified or situation-specific monitoring.</p> <p>Use independent assessors, be creative.</p> <p>Time to rethink therapeutic strategies regarding “traditional treatments” and ongoing protocolized trials. We need to involve physicians, regulatory, care-takers and patients into decision making processes. We need to assess what is necessary to assess function, disease progression and preference.</p> <p>Specific concerns and <i>potential solutions</i> related to patients hospitalized with Heart Failure.</p>

Biomarkers support

<i>Some issues from the Workshop</i>	<i>Questions/Challenges</i>	<i>What about tomorrow</i>
<p>Many heart failure therapies were introduced in the pre-clinical trial era.</p> <p>BNP may improve speed and accuracy of diagnosis in trials.</p> <p><i>Physicians</i> require evidence of the clinical validity and utility of biomarker-based tests in order to integrate and properly consider these options.</p> <p><i>Regulators</i> require this information to ensure the quality and efficacy of biomarker-based tests despite a «tsunami» of data on biomarkers in HF.</p> <p>Novel biomarkers will only see clinical adoption if their addition to the current chronic HF armamentarium improves clinical outcomes at a reasonable cost.</p> <p>They all should be clinically relevant in: hospitalisations for HF, causes of hospitalisation (co-morbidities, non adherence etc), worsening Heart Failure without Hospitalization , No. of hospitalisations/year, Patients' recurrent journeys to and from the hospital, recurrent morbid events.</p>	<p>Which endpoint beyond mortality and dyspnea? Is a particular biomarker measurable?, does it aid management?, what does it add?</p> <p>How much multi-organ damage is pathognomonic and prognostic? How much can biomarkers help to interpret signals of benefit or harm.</p> <p>Validation of BMs requires successful therapies first, to even have a chance to develop acceptable surrogate markers for regulatory approval: how to exit from this circle logic?</p> <p>Why don't we trust our judgment? How much can biomarkers add to our judgement or standardize decisions processes?</p> <p>The rigor required of clinical trials is a delicate balance between a well-defined narrow population (with limited applicability) and the quest for uncontrolled "real life data".</p> <p>In the electronic age, a complete review of all patients prescribed a new drug of therapy new drugs is now possible and the added value of the Post Marketing Pharmacovigilance machine should be re-assessed. Incentives for investment in heart failure trials will be created. Complex regulatory processes will be streamlined, accelerated and simplified. With success, more companies will invest in heart failure research.</p> <p>With the fulfillment of these expectations, industry-sponsored cardiovascular trials will thrive in the next 15-20 years .</p>	<p>Can data on biomarkers become more relevant to include as efficacy & safety end-points (and guide Phase IIb)? How much could be required of biomarkers in the development studies of new pharmaceutical approaches; in the preventive diagnosis, in the evaluation, and in the effective treatment of HF?</p> <p>How and when to use biomarkers as a helper/support to clinical decisions? What target sub-populations of heart failure patients can potentially benefit from a new intervention? Can clinical trials be improved and streamlined? What will politicians, regulators and payors be asked to do in the future? What will be their needs?</p> <p>Prioritize HF : create a policy to increase societal awareness of the epidemic of heart failure .</p> <p>Incentivize HF research : given the magnitude of the problem, and the risk adverse nature of industry, new incentives to encourage development of drugs in heart failure (similar to those in the GAIN Act) for antibiotics should be developed.</p> <p>Optimize the environment for the conduct of clinical trials and reduce bureaucratic burden. Increase transparency and create guidelines for reimbursement negotiations.</p> <p>Develop a quality assessment tool to assess effectiveness of EMA processes, to re-evaluate usefulness and efficacy.</p>

Industry needs

<i>Some issues from the Workshop</i>	<i>Questions/Challenges</i>	<i>What about tomorrow</i>
<p>No “one size fits all” approach. Dyspnea improvement appears to be a weak endpoint: negative in 6 out of 8 trials. Balancing rigid interpretation of data and methodology, with the humble recognition that AHF is still a field of ‘unknown unknowns’ --“consequences of lack of consensus and /or unwillingness to accept some uncertainties means that patients are denied potentially useful treatments”.</p> <p>The “Real Risk” is the future of research in AHF... If measures which may be of high relevance to patients and physicians are not considered in the assessment of new AHF therapies, then new therapies which may provide such benefits may not reach the patients in need.</p> <p>Ongoing research in AHF will be limited if the only way to assess therapy is by having to conduct an outcome trial as the point of entry- especially given the absence of a standard of care today which has this profile.... Clinicians will identify and address hurdles that prevent optimal care in patients with heart failure.</p>	<p>The challenge for industry: “promising drugs that are not being made available because of the expense and risk of developing them”.</p> <p>How do we get consensus on optimal background therapy when evidence is limited?</p> <p>How do we show incremental benefit on signs and symptoms when background therapy works? Is dyspnea really a rigorous or relevant endpoint for new therapies given background treatments work?</p> <p>Are intermediate endpoints of prevention of worsening of clinical status of more relevance? . What is the role and validity of recurrent hospitalization as an efficacy endpoint? Should re-hospitalization be an efficacy endpoint in AHF given the impact of extrinsic (non-HF) factors?</p> <p>Clinicians will identify and address hurdles that prevent optimal care in patients with heart failure.</p> <p>Will clinicians and non-profit organizations continue to work to address open issues in heart failure therapy and management - especially where there is no commercial interest?</p>	<p>Sequential collaborative, interdisciplinary, holistic and patient focused /centered approach desired and around: Payers, Industry, Reimbursement, Guideline Committees, Physicians, Health Authorities.</p> <p>The Industry for HF trials in the future can: Target sub-populations of heart failure patients who can potentially benefit from a new intervention; improve and streamline conduct of trials.</p>

Economic requirements

<i>Some issues from the Workshop</i>	<i>Questions/Challenges</i>	<i>What about tomorrow</i>
<p>Definition of value:</p> <p>a) Based on value-for-money, such as the health outcomes per dollar achieved: “value depends on results, not inputs. Value in health care is measured by the outcomes achieved, not the volume of services delivered, and shifting focus from volume to value is a central challenge” (<i>Porter M. What is value in health care? NEJM 2010; 363(26):2477-2481</i>).</p> <p>b) Based on broader values such as the importance or desirability that patients (or society) place on a health state.</p> <p>Since value is defined as outcomes relative to costs, it encompasses efficiency.</p> <p>Cost reduction without regard to the outcomes achieved is dangerous and self defeating, leading to false “savings” and potentially limiting effective care.</p>	<p>Avoid market “failures.</p> <p>Emerging needs = “advanced” regulation.</p> <p>Ensure health care system sustainability.</p> <p>How worthwhile a technology is, how defensible the tough bits of the decision are, how tolerant of uncertainty the committee ought to be, how inter-personal comparisons?</p> <p>The choice of a certain definition of value plays a central role in the identification of the analysis perspective as well as the relevant outcomes.</p> <p>Many countries have established mechanisms to base their decisions on value produced by new technologies including the degree of innovation.</p> <p>Multi-criteria decision-making, is a promising tool to inform decisions based on a broad and composite concept of value.</p>	

Payer needs

<i>Some issues from the Workshop</i>	<i>Questions/Challenges</i>	<i>What about tomorrow</i>
<p>The evaluation of a patient with suspected heart failure entails more than determining whether or not the syndrome is present – it also requires an identification of the underlying abnormality of the heart.</p> <p>Higher prevalence in elderly (potential impact of co-morbidity and co-medication). Great heterogeneity in different countries/structures in diagnostic and therapeutic approaches to HF.</p> <p>To determine the most clinically effective and cost-effective diagnostic algorithms it should be considered: symptom or sign, clinical features, electrocardiography , natriuretic peptides, echocardiography.</p> <p>Other costs include cardiac imaging (TOE, CRM, SPECT, PET). Other investigations are cardiac catheterization, genetic testing.</p>	<p>Higher prevalence in elderly (potential impact of co-morbidity and co-medication).</p> <p>Collaboration and communication between stakeholders (research centers, patients and physicians associations, regulators, payers and pharmaceutical industry).</p> <p>Design together (Regulators, Payers, Manufacturers, University, Patients) clinical trials to obtain homogenous and forecasting decisions.</p> <p>Stimulating high quality research defining consistent and transparent quality standards.</p> <p>Harmonizing clinical trial procedures, defining endpoints for added clinical benefit in view of HTA; promoting “scientific advice” model in the process of R&D shared by the Regulator and the Payer.</p>	<p>Prioritize HF: create policy to increase societal awareness of the epidemic of heart failure.</p> <p>Incentivize HF research.</p> <p>Given the magnitude of the problem, new incentives to encourage development of drugs in heart failure (similar to those in the GAIN Act) for antibiotics should be developed.</p> <p>Optimize the environment for the conduct of clinical trials and reduce bureaucratic burden.</p> <p>Increase transparency and create guidelines for reimbursement negotiations.</p> <p>Develop a quality assessment tool to assess effectiveness of EMA processes, to re-evaluate usefulness and efficiency.</p>

Regulatory approach

Some issues from the Workshop	Questions/Challenges	What about tomorrow
<p>Drug development in the centralized regulatory system, scientific advice, qualification procedures.</p> <p><i>preclinical development:</i> pharmacological screening , mechanism of action, predict activity/safety.</p> <p><i>clinical development:</i> verify mechanism, dose-response, proof of concept, enrich population, surrogate endpoint.</p> <p><i>drug utilisation:</i> optimise target population, guide treatment regimen.</p> <p>Criteria to assess efficacy in HF: <i>AHF:</i> -In Hospital and 4 wks mortality -Depending on the indications claimed, long term mortality and duration of hospitalisation - Improvement in hemodynamic state and symptoms (<i>categorical composite</i>) -Relief of other manifestations of AHF including need of inotropic support and vasodilators <i>CHF:</i> -Mortality, morbidity -Primary composite</p>	<p>Need clarity on symptom (PROM) control— methods, endpoints, means of measurement. Need also a guide for consistent conduct of clinical trials in HF.</p> <p>Academic Guidelines have insufficient detail of usefulness of PRO evaluation or data supporting PRO based Rx and relation to outcome.</p> <p>Most trials study single compounds. Few HF trials examine treatment strategies. There is need to examine this area.</p> <p>A number of already existing regulatory activities can support the development of products in line “real-time” with science.</p> <p>Early discussion with EMA on alternative/adaptive designs, endpoints, models.</p> <p>Increased interaction between regulators and learned societies to facilitate updating of science in regulatory procedures.</p> <p>Open issues: Different economical value of the mortality/morbidity and the functional end-point.</p> <p>Reimbursement value of CV drugs is too low compared to cancer, HIV, Hepatitis. Haemorrhage of budgets from CV to other therapeutic areas.</p> <p>Need to identify and define clinical entities besides acute and chronic heart failure.</p> <p>Definition of clinically meaningful end points that may also be of importance for payers.</p> <p>Definition of standardised composite end points.</p>	

Considerations

Strategies and management in heart failure require a strong and continuous collaboration among regulatory, clinical, industry, economy, payment experts and, not the least, the patients.

Heart failure represents an increasing burden on patient health and National health expenditures. 26 million patients are affected by heart failure, with an estimate of 6.5 million patients in Europe and 5.8 million in the USA. It is the primary cause of 1 million hospitalizations with a mortality risk after hospitalization of nearly 30%. The burden of heart failure is expected to continue to rise with the aging of the population.

Heart failure, in its acute and chronic development represents an urgent need to identify advanced diagnostic approaches, to better understand the behavior and needs of the single patient, and to more appropriately identify the risk, evaluate and design effective treatment strategies and to allocate adequate economic resources to this important clinical condition.

A multidisciplinary approach and the inclusion of the patient needs in all processes will open a best return of the cost/effectiveness of reliable medical approaches, and allow further optimization of the cooperation among the stakeholders in identifying the ways to better support sustainable economic approaches to the HF management.

Disease management is increasing the need to approach pathologies with a therapy that is more demanding and more complex than the already composite but without a defined pharmaceutical approach. This complexity requires a new clinical strategy for future clinical trials, that will go beyond the traditional pharmaceutical approach over the last 20 years. There is a need to go from a single molecule to a larger medical strategy. This is expected to modify times, arenas and relationships among patients, clinicians, industry and payers and that will change the responsibilities of each stakeholder. The drug approval and the definition of the reimbursement processes will go together and both of them will be posed in advanced steps among the other urgent scientific approaches for the clinical and industry experts.

The research and development of a new drug still constitutes a very risky, long and costly investment. The risk is to widen the gap between patients' expectations and care needs on one side and the existing innovative therapies on the other.

There is an increasing necessity to go from passage of single drug licensing to the so called *adaptive licensing*. This not only for the syndrome of heart failure, but for other complex syndromes as well. The adaptive licensing will provide an anticipated approval, from 3 to 8 years, with the availability of a drug for a limited number of highly monitored patients. The anticipated use in the II phase of the drug evaluation together with the other clinic expertise phases, introduces a large amount of results and information. After the first approval, the second and third approval phases represent a free introduction of the individual commercial use of the drug. This may be one answer to the long time and many factors to be studied in order to make progress in the treatment of HF. The use of an adaptive licensing scenario, opens a productive feedback in the information for further evaluation. On that basis, thank to the input of all the stakeholders, it is possible to build up a new and more flexible model to translate this to reality in this historical time for the medicine.

Many priorities commonly shared by the regulatory, clinic, and industry participants of the Workshop, such as biomarker identification, and the need to define useful endpoints both for better understanding the underlying pathology and the possibility to develop an effective therapeutic approach, could open a promising way in this sector.

The workshop is confirming a proactive role of AIFA in the study and development of the more problematic and complex issues in the regulatory sector. The workshop can represent a prototype of a series of meetings devoted to debate unmet needs with all stakeholders towards a tentative roadmap for the future.