Rigshospitalet
The Heart Centre

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

REGION

Ethical Aspects & Approval Procedures in H2020 Clinical Trials: challenges & best practice

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GLOBAL EXCELLENCE IN HEALTH

Innovation Fund Denmark

THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
HORIZON 2020

SCIENCE Trial

Stem Cell therapy in **I**sch**E**mic **N**on-treatable **C**ardiac diseas**E**

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THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
HORIZON 2020

Cardiology Stem Cell Centre (CSCC)

Cover all steps in clinical stem cell trial initiation

- Pre-clinical development
- Regulatory Affairs
- Production, QA, QC
- Clinical Trials

CSCC background

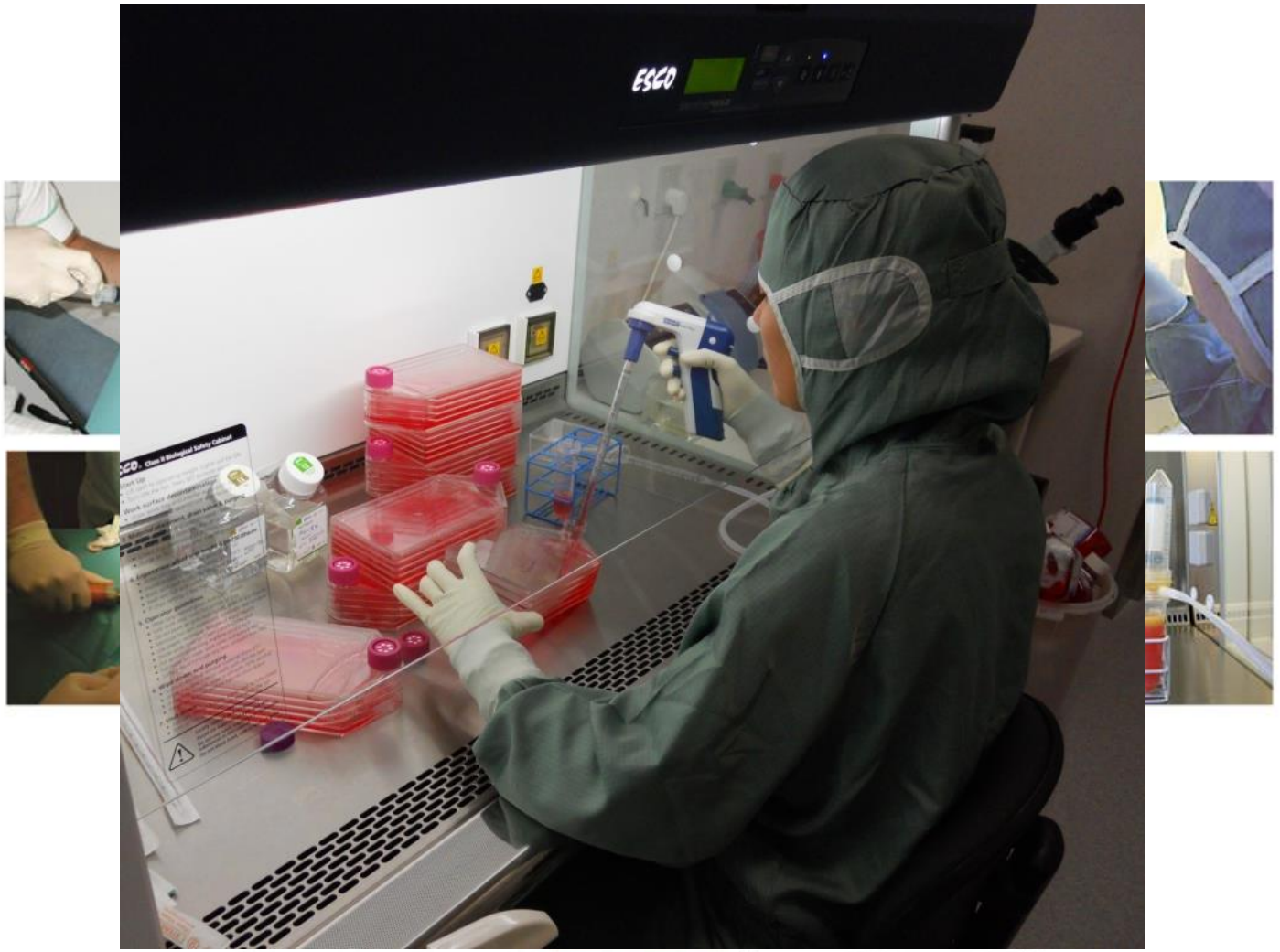
3 clinical studies with ***autologous*** mesenchymal stromal cells in patients with chronic ischemic heart disease w/wo heart failure

- Copenhagen MSC Study – Refractory angina (Phase I)
  - MSC + VEGF
- Copenhagen MSC-HF Study – Heart failure (Phase II)
  - MSC
- MyStromal Cell Trial – Refractory angina (Phase II)
  - ASC +VEGF

Stem cells from bone marrow and adipose tissue

MSC

ASC



Mesenchymal **S**tromal **C**ell treatment of Patients with chronic ischemic heart disease and heart failure

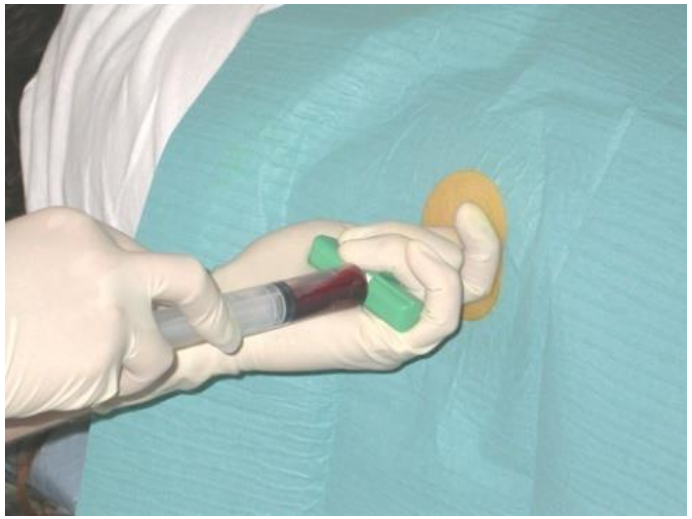
MSC HF Trial I

Double-blind placebo-controlled study

60 patients with chronic ischemic heart disease with heart failure

MSC isolated from bone marrow

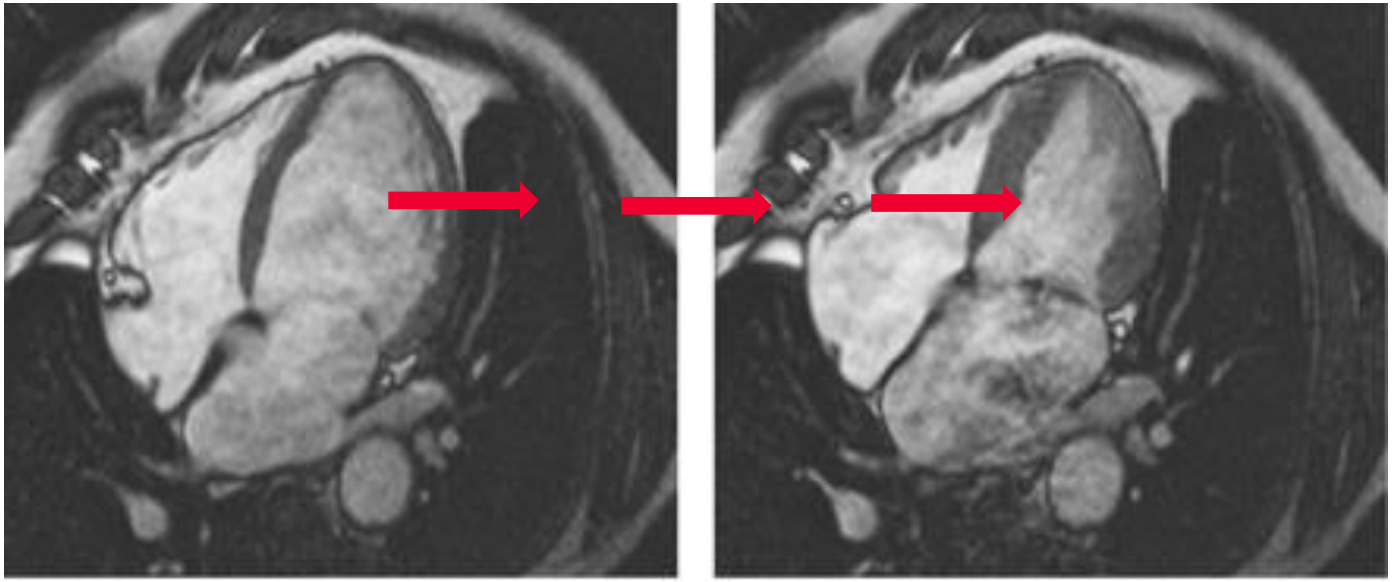
Randomised 2:1 to MSC or placebo (saline)



Mathiasen et al. Eur Heart J. 2015 Jul 14;36(27):1744-53

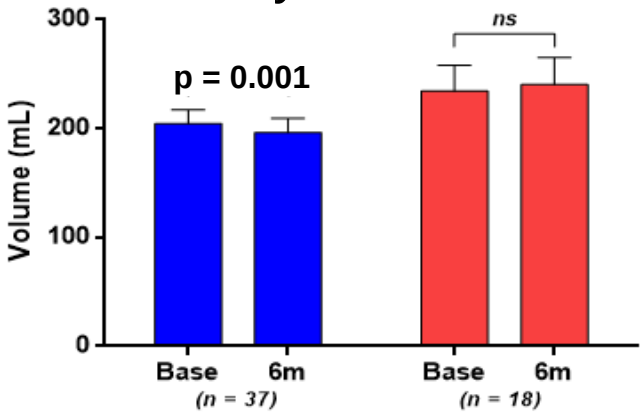
Primary endpoint

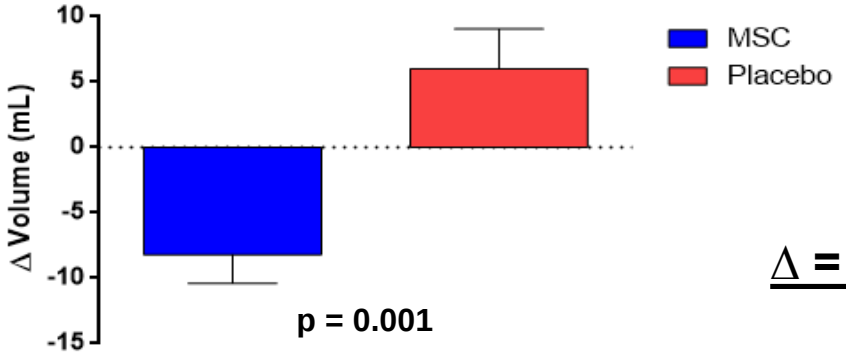
Changes in left ventricular end-systolic volume



Results

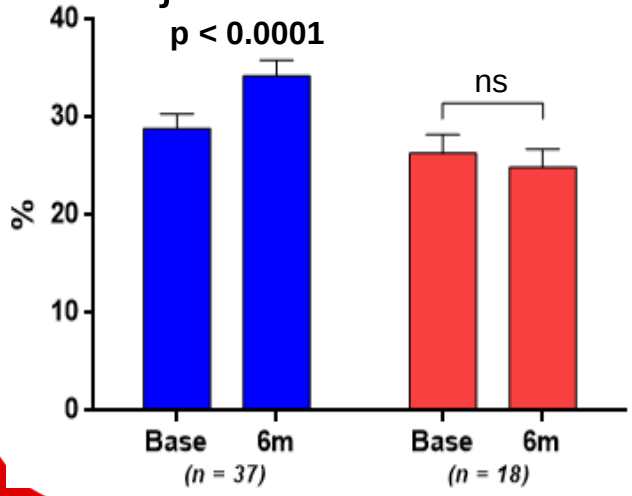
End systolic volume

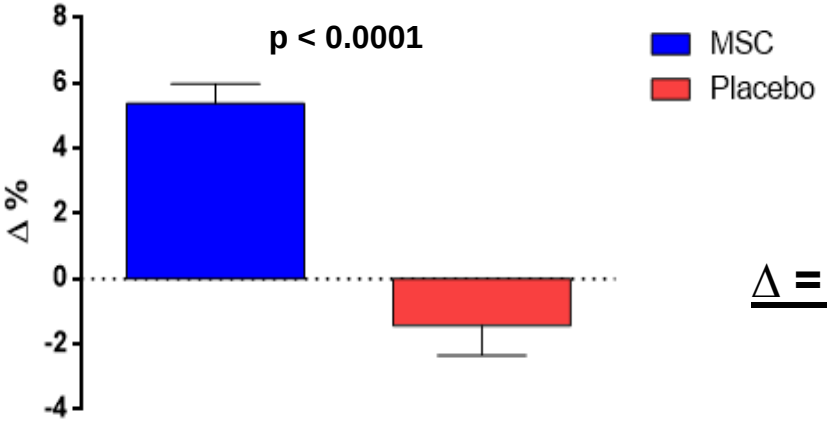




Δ = 14.2 mL

Ejection fraction





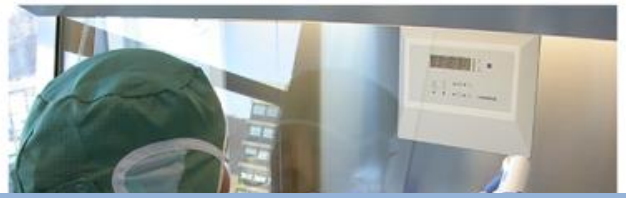
Δ = 6.8 %

Mathiasen et al. Eur Heart J. 2015 Jul 14;36(27):1744-53

(Mean + SEM)

3 clinical studies with manual production…..

- expansion of cells from 111 patients…..



Medium in a T-flask is changed in average

145 times for each patient

Stem cell therapy – what have we learned?

To transfer stem cell therapy into a more generel therapy

-

then it has to be logistically simple to perform and conduct

New manufacturing technology

Cardiology Stem Cell Centre

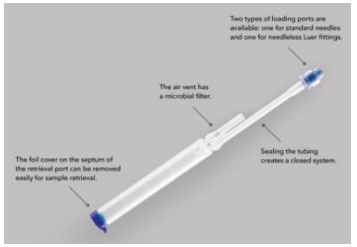
- automated expansion
- human growth supplement
- cryo storage

21 T1000 flasks
or
280 T75 flasks

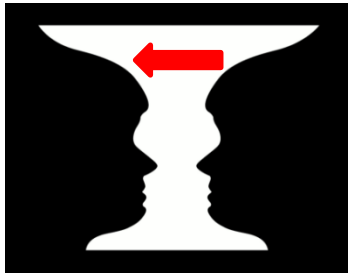
Stemulate

Area: 2.1 m^2
1 bioreactor = **280** T75 flasks

1. Healthy donors
2. Standardised and reproducible production
3. Increased yield
4. Less labor intensive and time saving
5. Off-the-shelf product
6. Feasible
7. Lower costs



CellSeal



Allogeneic

Aim project

The overall aim of the SCIENCE project is to implement an effective stem cell-based therapy to improve myocardial function in patients with ischemic heart disease (IHD) and heart failure.

SCIENCE – Clinical trial

Design

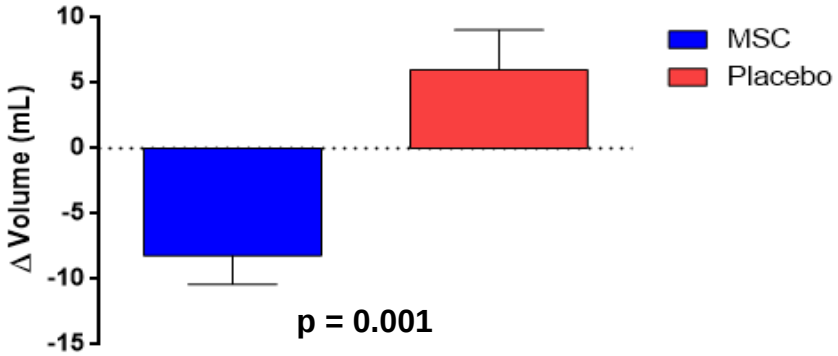
The trial is a double-blind multi-centre placebo-controlled trial with a ***2:1 randomisation*** of allogeneic adipose derived stem cells (CSCC_ASCs) vs placebo in patients with severe ischemic heart failure.

Patient population

The study will include 138 patients with stable ischemic heart failure with a left ventricular ejection fraction ≤ 45 %, New York Heart Association Heart Failure Class (NYHA) 2 -3 and on maximal tolerated anti-congestive therapy.

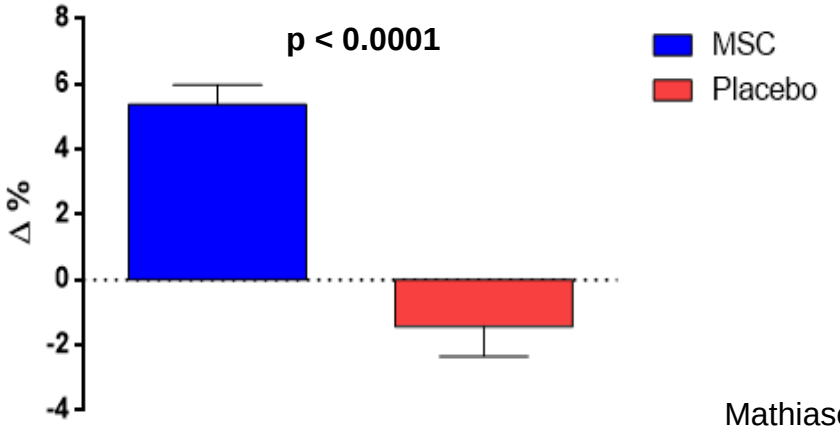
Power calculation

End systolic volume



Δ = 14.2 mL

Ejection fraction



Δ = 6.8 %

Mathiasen et al. Eur Heart J. 2015 Jul 14;36(27):1744-53

(Mean + SEM)

SCIENCE – Clinical trial

Power calculations with 80 ASC and 40 placebo patients

Which difference to detect with > 80% power
Difference in ESV 8.2 mL (Estimated SD 15 mL)
Difference in EF: 2.8 % (Absolute %) (Estimated SD 5 %)

The Ethical Committees and Competent Authorities

will look at your power calculation

Difference in EF: 3.2 % (Absolute %) (Estimated SD 5 %)

Which difference to detect with > 90% power and with higher SD
Difference in ESV 12.7 mL (Estimated SD 20 mL)
Difference in EF: 5.1 % (absolute %) (Estimated SD 8 %)

SCIENCE – Clinical trial

Cell production

The investigational medicinal cell product ***CSCC_ASC*** will be produced in Cardiology Stem Cell Centre, Rigshospitalet, Copenhagen, Denmark which is an approved Good Manufacturing Practise facility in Denmark.

The final cell products will be stored in dry-storage nitrogen containers at Rigshospitalet until transportation to the clinical departments by a courier approved for transportation of cell products for clinical use.

The clinical departments will receive the final cell products in batches of 6 (***4 CSCC_ASC and 2 placebo***) to be stored locally in either dry-storage or vapour nitrogen containers until treatment of the patients.

SCIENCE – Clinical trial

Cell treatment

The investigational medicinal product CSCC_ASC will be thawed and prepared for injection immediately before treatment.

Each patient will receive 12-16 injections of 0.3 – 0.4 mL investigational product (100 million ASCs or placebo) directly into the myocardium using the NOGA XP® system (Biological Delivery System, Cordis, Johnson & Johnson, USA).

SCIENCE – Clinical trial

Inclusion criteria

- 30 to 80 years of age
- Signed informed consent
- Chronic stable ischemic heart disease
- Symptomatic heart failure (NYHA II-III)
- LVEF ≤ 45% on ECHO, CT or MRI scan
- Plasma NT-pro-BNP > 300 pg/ml (> 35 pmol/L)
- Maximal tolerable heart failure medication
- Medication unchanged two months prior to inclusion/signature of informed consent. Changes in diuretics accepted
- No option for percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)
- Patients who have had PCI or CABG within six months of inclusion must have a new angiography less than one month before inclusion or at least four months after the intervention to rule out early restenosis
- Patients cannot be included until three months after implantation of a cardiac resynchronisation therapy device (CRTD) and until 1 month after an ICD unit

SCIENCE – Clinical trial

Exclusion criteria I

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  in these patients.
- If the patient is expected to be candidate for MitraClip therapy of mitral regurgitation in the 12 months follow-up period.

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Take into your consideration whether you have the relevant inclusion and exclusion criteria.

HORIZON2020 do not consider these criterias

but

The Ethical Committees and Competent Authorities look carefully on these criterias in relation to relevant treatment

SCIENCE – endpoints

The *primary endpoint* is change in left ventricle end-systolic volume (LVESV) at 6 months follow-up between CSCC_ASC and placebo treated measured by ECHO.

The *secondary endpoints* are:

- Safety evaluated by development of allogeneic antibodies and incidence and severity of serious adverse events and suspected unrelated serious adverse events at 12 months follow-up
- Laboratory safety measurements 1, 3 and 6 months after treatment
- Changes in left ventricular ejection fraction (LVEF), end-diastolic volume and myocardial mass at 6 months follow-up
- Changes in NYHA, CCS, Kansas City Cardiomyopathy Questionnaire, Seattle Aniga Questionnaire, 6 min walking test
- Echocardiographic measures (Global strain %, LA volume, e', s') serum NT-pro-BNP

SCIENCE – endpoints

The *secondary endpoints* are

A combined endpoint of

- D… g
  in… cause
  o… fter
  tr…
- D…
  h…ing of a bi-ventricular pacemaker, hospitalization because of ventricular tachycardia or fibrillation and 1, 2 and 3 years after treatment

The Ethical Committees and Competent Authorities

will look at your endpoints in relation to your

patient population and treatment

Regulatory approval/clinical trial application ?

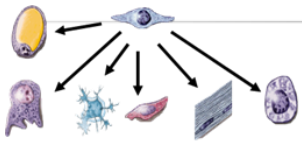
Voluntary Harmonisation Procedure

or

Individual national submission to Competent Authorities

Voluntary Harmonization Procedure

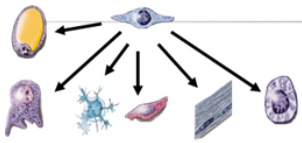
Name	Country
Jens Kastrup (Cardiology Stem Cell Centre, Copenhagen)	Denmark
Annette Ekblond (Cardiology Stem Cell Centre, Copenhagen)	Denmark
Martin Bergmann (Cardiologicum Hamburg)	Germany
Wojtek Wojakowski (Medical University of Silesia, Katowice)	Poland
Bojan Vrtovec (Ljubljana University Medical Centre)	Slovenia
Steven Chamuleau (UMC Utrecht)	Netherlands
Mariann Gyöngyösi (Vienna)	Austria
Karsten Vrangbæk (Copenhagen University)	Denmark
Hans Keiding (Copenhagen University)	Denmark
Adrian Abbotts (Terumo BCT)	Belgium
Henk Snyman (Cook Medical)	US/Denmark



HMA
Heads of Medicines Agencies

Approvals from ethical committees are not part of VHP

Doc. Ref.: CTFG//VHP/2013/Rev1
June 2013



The following information was forwarded to VHP July 2015:

1. Core CTA EudraCT form (general information for all Member States)

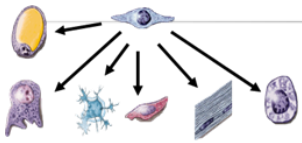
2. Study (clinical) protocol including synopsis

3. Investigator's brochure

4. Investigational Medicinal Product Dossier

5. IMP additional information: manufacturing authorisation (including microbiological quality control); GMP compliance certificate; Authorisation for Tissue Centre Activity (June 2015).

6. Copy/summary of any scientific advice from any competent authority or EMEA



30th September:

LIST of 35 GNAs (Grounds for Non-Acceptance)		
18	Quality (manufacturing)	
14	Clinical Trial	
3	Viral safety	

10 days to answer

-what do authorities take an interest in ???

18 GNAs related to Quality
Microbiological control during
Control of raw materia
Stability of the
Throu

VHP considered and accepted all answers

3 GNAs related to Viral Safety
The sponsor should clarify the origin of the re and provide information about virus an
The sponsor sh cryoprecip If n rtate
turing process of the platelet step. ent, the pool size for the platelet lysate donors per pool

VHP considered all answers:

Pool size for all blood products used adjusted;
maximum16 donors pooled

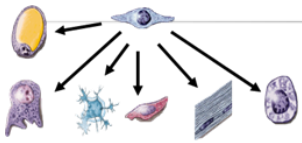
-what do authorities take an interest in ???

14 GNAs related to Clinical Trial
Data Monitoring Board
Helsinki Declaration
Procedure for unbli
Reporting of
Incl
P controlled design (safety for the placebo group)

Scientific validity is essential!

VHP considered all answers

The GNA about the placebo controlled design remained…..



A second completely new VHP was submitted December 201

GNA No.:	List of GNA
1	
2	

ation for

April 4, 2016

Following your reply of the 06.03.2016 concerning the grounds for non-acceptance/request for further information, sent to you on 02.03.2016 the participating Member States have unanimously agreed that all points have been sufficiently addressed. The VHP811 (VHP2015182) is closed.

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Next steps

- Preparing documents for national submission to Competente Authorities and Ethical Committees
- Each participating centre submitted nationally
- New additional request from national CA – antibody screening against donor cells
- Many different national EC approval processes

Ethical Committee comments - Germany

1. Safety of allogeneic stem cell product
2. Sample size should be elaborated on:
   standard error and power should be precise etc.
3. Stopping rules for the trial (SUSAR, SAE etc.)
4. DSMB
5. Biobank – amount of samples for number of years
6. Anonymizing data

Ethical Committee comments - Austria

1. Better description of the randomization
2. Blinding and emergency unblinding
3. Quality of the data: is there any centralized core facility?
4. Data analyze strategies
5. Statistics: for each end-point an appropriate statistical test should be described
6. A drop-out rate of 15% in the first 6 months is rather high
7. Detailed termination criteria
8. information about handling of inspections or audits is requested
9. Sample size should be elaborated on: standard error and power should be precise etc.
10. Biobank – (location, responsible persons, temperature for plasma freezing)
11. Medication – permitted changes

Ethical Committee comments - Denmark

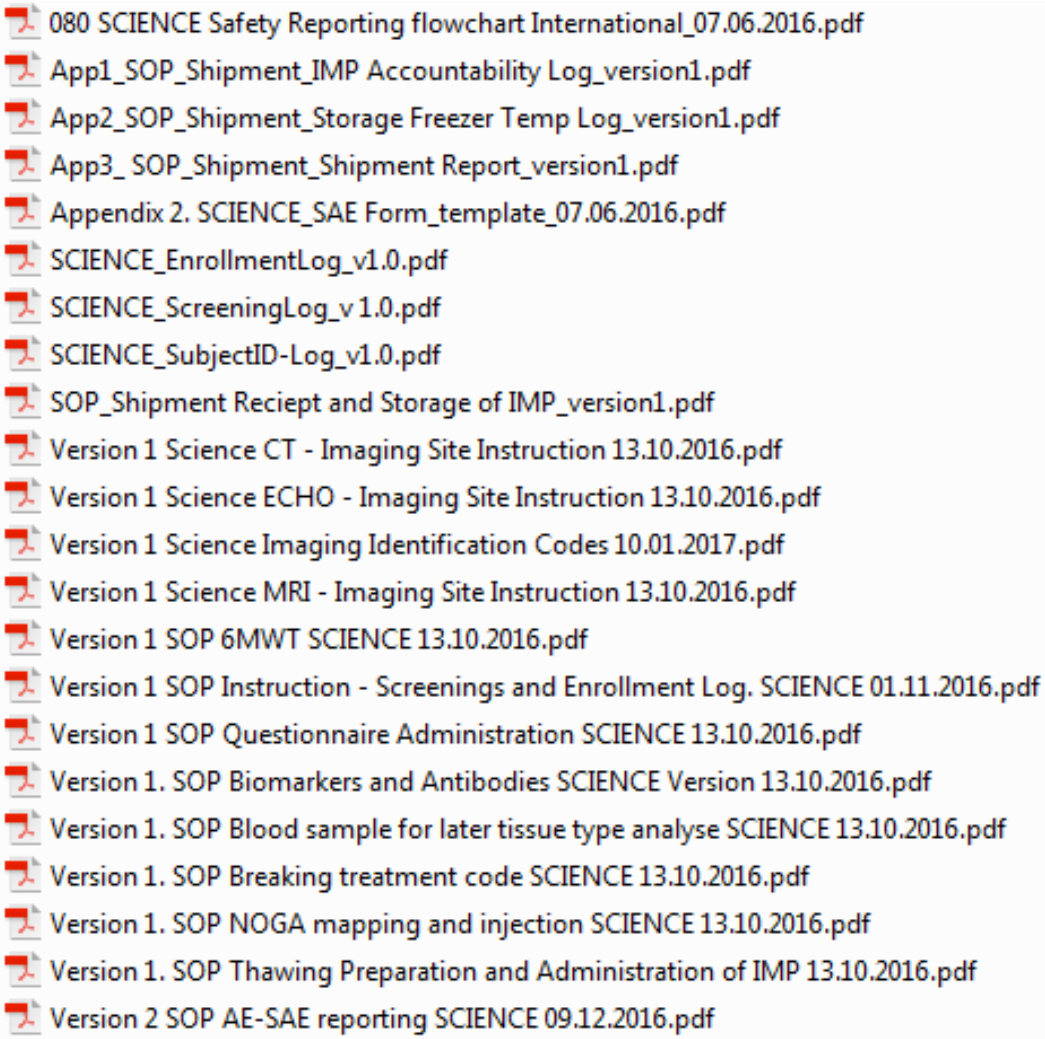
1. Procedure for information and obtaining informed consent

The Ethical Committee

had previously approved the safety study,

which was the background for the SCIENCE trial

Ethical Committee comments – prepare SOPs



The net result

Horizon2020 grant January 1, 2015

Initiation of SCIENCE clinical trial

was

postponed to January 19, 2017