The DETECT study: A two-stage, prospective, observational, cohort study in scleroderma patients to evaluate screening tests and the incidence of pulmonary arterial hypertension and pulmonary hypertension

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Introduction and rationale

- Pulmonary manifestations of systemic sclerosis (SSc) are a leading cause of mortality and late stage disease morbidity[1]
  - 15–20% of SSc patients develop pulmonary arterial hypertension (PAH)[2]
  - Median survival of SSc patients with untreated PAH is particularly poor: an estimated 1.5–2.0 years following diagnosis[3]
- PAH associated with SSc is typically diagnosed late, when other SSc symptoms are well established
- Early detection of PAH associated with SSc is considered essential to allow for optimal patient management[4]
- The standard confirmatory test for PAH and more broadly pulmonary hypertension (PH) is right heart catheterization (RHC)[5]
- The objective of the DETECT study is to improve the management of PAH and PH in SSc by validating simple, cost-effective, accessible and reliable screening tools

Objectives

Primary objectives

- To determine the discriminatory and predictive ability of single screening tests for PAH in SSc by means of comparison with RHC, the current gold standard diagnostic test
- To determine the discriminatory and predictive ability of single or multiple tests for screening of PAH in SSc patients

Secondary objectives

- The two primary objectives will be repeated for the broader PH population
- The incidence of PAH and PH in the cohort of SSc patients will be estimated during the 3-year longitudinal phase

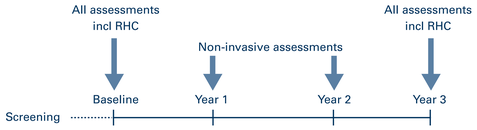
Exploratory objectives

- To assess the correlation between changes in screening test results and changes in measures of clinical status during the follow-up period
- To investigate the association between potential prognostic factors and development of PAH and PH during the follow-up period

Methods

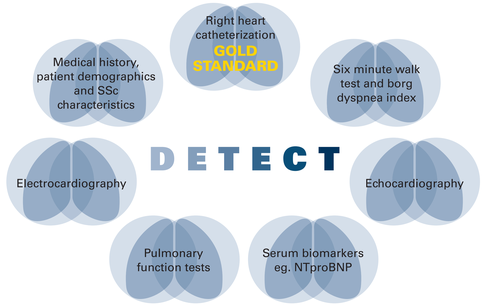
Study design and timelines

- The DETECT study, which started in 2008, is a prospective, observational cohort in two stages:
  - Cross-sectional stage (results expected in 2010)
    - To evaluate different screening tests for PAH and PH in SSc patients, versus RHC
  - 3-year longitudinal follow-up (results expected in 2013)
    - To evaluate the incidence of PAH and PH in a cohort of SSc patients
    - To determine the association of potential prognostic or risk factors and the development of PAH/PH during the follow-up period



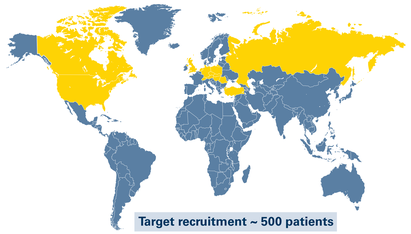
- No investigational medicinal product will be used in this observational study

Screening tests evaluated for their ability to detect PAH/PH in SSc patients



NTproBNP: N-terminal prohormone B-type natriuretic peptide

Participating countries (number of sites) in the DETECT study



USA (24), Canada (10), Austria (2), Czech Republic (1), Germany (11), Hungary (2), Netherlands (1), Poland (1), Romania (1), Russia (1), Slovakia (1), Turkey (5), Switzerland (3), UK (1)

Study subjects

- Inclusion criteria
  - Male or female patients aged ≥18 years
  - Patients with SSc as diagnosed by the American College of Rheumatology (ACR) criteria[6]; including patients with other connective tissue diseases who, in parallel, meet the ACR criteria for SSc
  - SSc disease duration >3 years from onset of first non-Raynaud's symptom
  - Diffusing capacity of the lung for carbon monoxide <60% of predicted
- Main exclusion criteria
  - PH confirmed by RHC before enrollment, i.e. mean pulmonary arterial pressure ≥25 mmHg at rest or ≥30 mmHg during exercise, independent of pulmonary capillary wedge pressure[5]
  - RHC within the 12 months before enrollment
  - Use of endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostanoids, or experimental PAH/PH therapies ≤6 weeks prior to enrollment and/or for a total of >6 weeks during the 12 months prior to enrollment
  - Forced vital capacity <40% predicted
  - Renal insufficiency
  - Previous evidence or diagnosis of clinically relevant left heart disease and other relevant cardiac conditions
  - Pregnancy
  - Patients unlikely to be available for annual follow up over an anticipated 3 years of study

Statistical methodology and analyses

- Analyses of data from the cross-sectional stage will include:
  - Description of demographic and baseline disease characteristics of patients
  - Evaluation of screening tests (individually or in combination) versus RHC
    - Receiver operating characteristic curve analysis (sensitivity, specificity, optimal rule-in and rule-out values and predictive values)
    - Multivariable logistic regression analysis
- Analyses of data from the longitudinal follow-up will include:
  - Estimation of the cumulative proportion of patients with confirmed PAH or PH following 3 years (or earlier in cases of withdrawal) assuming binomial distribution
  - Multivariable logistic regression analysis to investigate the association of potential prognostic risk factors and PAH/PH occurrence

Visit and assessment schedule

	Cross-sectional follow-up		Longitudinal follow-up		
	Screening	Baseline	Year 1	Year 2	Year 3 or earlier*
Informed consent (obtained before any invasive procedure)	✓	–	–	–	–
Check of eligibility criteria	✓	–	–	–	–
Demographics	✓	–	–	–	–
Medical history	✓	–	–	–	–
PFT: DL_{CO}/VA, FVC, FEV_1, TLC, residual volume	✓	–	✓	✓	✓
Concomitant medication	–	✓	✓	✓	✓
SSc characteristics	–	✓	✓	✓	✓
Serum analysis by central lab	–	✓	–	–	✓
Serum storage by central lab	–	✓	✓	✓	✓
Physical examination	–	✓	✓	✓	✓
Echocardiography	–	✓	✓	✓	✓
Electrocardiogram	–	✓	✓	✓	✓
RHC**	–	✓	–	–	✓
6MWT, Borg dyspnea index	–	✓	✓	✓	✓
WHO FC (for patients diagnosed with PAH/PH)	–	✓	–	–	✓

** Earlier in case of suspected PH before Year 3 requiring RHC, or for patients predictably unable to stay in the study; **RHC performed as last test in order to exclude bias regarding any other test but not later than 2 months after the other tests; pregnancy is contraindicated*

Summary

- Pulmonary manifestations of SSc are a leading cause of mortality and late stage morbidity
- Early diagnosis and treatment of PAH in SSc patients is fundamental to optimal patient management
- The DETECT study is designed primarily to identify single or multiple screening tests for early detection of PAH in SSc patients
- The results of the DETECT study are expected to influence future PAH/PH screening guidelines and management of SSc patients
- A convenient non-invasive testing profile for PAH/PH in SSc patients would be expected to impact standards of care in a variety of clinical settings beyond SSc

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What is the application process to participate in the clinical trial?

- In general, recruitment of study sites has been completed
- Sites fulfilling all criteria and having a high patient enrollment potential may still, however, be considered for participation
- For more information please contact Fabrice.Kiefer@actelion.com