The ARAMIS trial

Anakinra versus Placebo, a Double Blind Randomized Controlled Trial for the Treatment of Acute Myocarditis

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on behalf of the ARAMIS investigators

Declaration of interest

Dr Mathieu Kerneis reports :

- consulting/lectures fees from Kiniksa, Eligo, Sanofi, Bayer.
- Research grants from Federation Francaise de Cardiologie and French Health Ministry
- Patent for the use of Abatacept in ICI induced myocarditis

All Disclosures are available on www.action-group.org

Study Organization

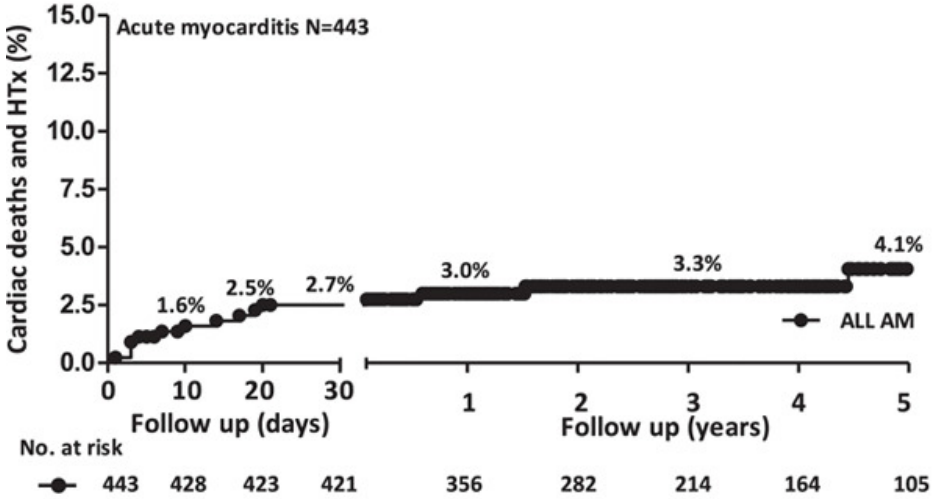
ARAMIS = Independent Academic Trial

- **Academic coordinating center :** Institute of Cardiology – ACTION Group – Pitié Salpétrière Hospital
- **Academic Sponsor :** Assistance Publique-Hopitaux de Paris
- **Academic Global Trial Operations :** URC Lariboisiere, ACTION Group, Paris
- **Academic Funding :** French Ministry of Health (PHRC)
- **Investigation Sites :** 6 academic centers in France
- All analyses were performed by an **independent academic statistician**

Background

Acute Myocarditis

Acute myocarditis (AM) is an **inflammation** of the myocardium that can cause **life-threatening events**



Ammirati et al. Circ 2018

Treatment of Acute Myocarditis

There is no evidence that a treatment targeting inflammation can improve outcome in « virus-negative » myocarditis patients[1]

A strategy of immunomodulation has not been evaluated in acute myocarditis patients with unknown viral replication (without EMB)[2]

Experimental studies and case reports suggest that blockade of the IL1-β pathway could be effective in AM [3,4]

Anakinra, an IL1-R antagonist, used in inflammatory diseases, has an acceptable **safety profile**[5]

[1] Frustaci, *et al.* EHJ 2009 - *TIMIC Trial*

[2] Tschöpe, *et al.* Nat Rev Cardiol 2021

[3] Lim BK, et al. Circ, 2002; [4] Cavalli G et al. Crit Care Med, 2016

[5] Brucato A et al., JAMA, 2016

Goal

To perform a pragmatic trial evaluating the inhibition of the IL-1β immune innate pathway with anakinra, to reduce the risk of clinical events in acute myocarditis patients

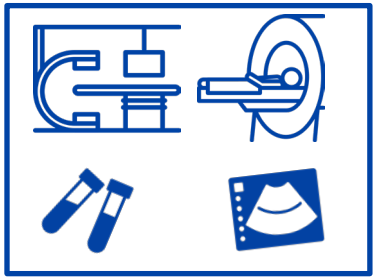
Study design

Study Design of the ARAMIS Trial

Randomized, Double Blind, Multicenter, Phase IIb trial

AM patients

Diagnosis



Within 72 hours

Treatment

R

- Placebo + Standard Therapy
- Anakinra 100mg sc o.d. + Standard Therapy

Follow-up

Number of days alive free of any myocarditis complications

28 days

- **Admission For a Suspected AM**
- **Confirmation of diagnosis and randomization**
- **Hospital Discharge**
- **Primary Endpoint**

Number of days considered for the Primary Endpoint

Inclusion/Exclusion Criteria

Inclusion

Myocarditis was defined as follows :

- Chest Pain
- **AND** modification of the ECG *or* elevated Troponin (at least 1.5 X ULN)
- **AND** CMR Lake Louise Criteria

AND Normal Coronary angiography or CTA in > 40 y/o *or* with CV risk factors

Exclusion

- < 18 y/o or > 65 y/o
- LV assistance
- Mechanical Ventilation
- **Any clinical suspicion of autoimmune, giant cell, eosinophilic, or sarcoidosis related myocarditis**
- Renal Failure
- Anti-TNF, CTC/NSAID use
- Malignancy

Endpoints

Primary Efficacy endpoint :
Number of days alive free of any myocarditis complications

HF requiring hospitalization
Chest Pain requiring medication
LVEF < 50% in TTE
Ventricular arrhythmia, VT or VF

within 28 days post hospitalization

Primary Safety endpoint :
Number of SAEs, including those potentially related to the drug :

Severe infection
ALT/AST > 10x ULN
Neutropenia < 1. 109/L
Renal failure (↑ 50% creat),
Thrombopenia < 50 000 mm3,
BARC> 3, Anaphylactic reaction
100% ↑ of LDL Cholesterol

Sample Size

Superiority trial

anakinra at the approved dosage of 100mg o.d + SOC (betablocker + ACE inhibitor)

vs placebo + SOC

↑ of the number of days free of myocarditis complications

> 1.5 day = clinically meaningful

SD of the 1°EP = 2.3

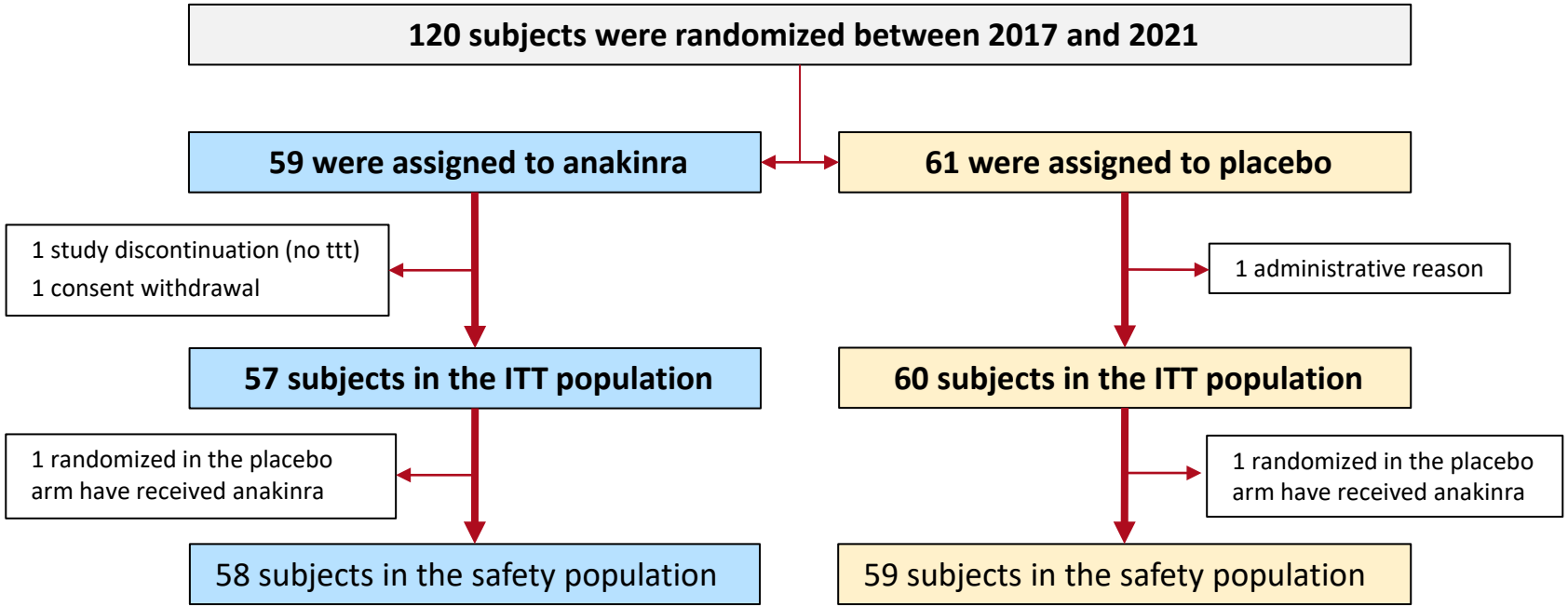
based on the AMPHIBIA registry (NCT04844151)

60 patients in each group

⇒ 80% power to demonstrate a 1.5 day difference

⇒ 5% two-sided significance level

Flow Chart


120 subjects were randomized between 2017 and 2021
59 were assigned to anakinra
61 were assigned to placebo
1 study discontinuation (no ttt)
1 consent withdrawal
1 administrative reason
57 subjects in the ITT population
60 subjects in the ITT population
1 randomized in the placebo arm have received anakinra
1 randomized in the placebo arm have received anakinra
58 subjects in the safety population
59 subjects in the safety population

Patient characteristics

Clinical Presentation (1/2)

	Anakinra N=57	Placebo N=60
Median Age, (Q1;Q3), yrs	28.0 (22.8 ; 38.1)	29.0 (23.2 ; 34.0)
Male — no of patients (%)	52 (91.2%)	50 (83.3%)
Current smoker — no. (%)	30 (52.6%)	30 (50.0%)
Past Medical History		
Prior myocarditis — no. (%)	1 (1.8%)	3 (5.0%)
Recent Bacterial infection— no. (%)	9 (15.8%)	6 (10.0%)
Recent Viral infection — no. (%)	25 (43.9%)	27 (45.0%)
Chest Pain — no.(%)	57 (100%)	60 (100%)
Dyspnea — no. (%)	4 (7.0%)	9 (15.0%)
Cardiogenic shock — no. (%)	1 (1.8%)	0 (0.0%)
Ventricular fibrillation — no. (%)	1 (1.8%)	0 (0.0%)
Conduction disorders — no. (%)	0 (0.0%)	1 (1.7%)
Clinical infectious syndrome — no. (%)	16 (28.1%)	18 (30.0%)

Clinical Presentation (2/2)

	Anakinra N=57	Placebo N=60
Troponin in fold increase of the ULN - Median (Q1;Q3)	**98 (33 ;194)**	**75 (22;217)**
CRP, mg/L - Median (Q1;Q3)	**37 (16;68)**	**23 (14;52)**
(NTpro)BNP, in fold increase of the ULN - Median (Q1;Q3)	0.9 (0.4;1.9)	0.5 (0.3;1.0)

Right or Left BB block — no. (%)	5 (8.8%)	4 (6.7%)
ST-segment elevation — no. (%)	**37 (64.9%)**	**39 (65.0%)**
ST segment depression — no. (%)	5 (8.8%)	7 (11.7%)

Coronary Imaging — no. (%)	48 (84.2%)	47 (78.3)

0 patient with EMB

Non Invasive Imaging

	Anakinra N=57	Placebo N=60
Left ventricular ejection fraction (TTE), %		
Median (Q1;Q3)	60 (50;61)	60 (50;60)
Min, Max	40, 73	35, 66
Ventricular dysfunction with TTE (LVEF<50%) — no. (%)	7 (12.3%)	5 (8.3%)
Regional wall motion abnormalities (TTE) — no. (%)	18 (31.6%)	16 (26.7%)
Left ventricular ejection fraction (MRI), %		
Median (Q1;Q3)	54 (50;60)	55 (52;60)
Min, Max	36, 72	38, 70
Ventricular dysfunction with MRI (LVEF<50%) — no. (%)	13 (22.8%)	10 (16.7%)

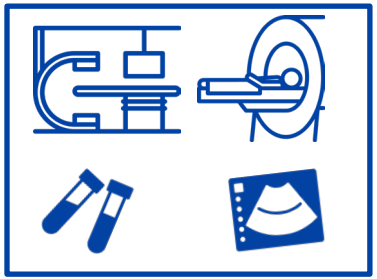
Absence of pericardial effusion — no. (%)	48 (85.7%)	47 (78.3%)

Results

Study course

AM patients

Diagnosis



R

Treatment

Follow-up

Composite Outcome 13.7%

2 days (1;3)

Min – Max = 0 - 4

2 days (1;3)

Min – Max = 1 - 6

28 days

CCU Admission For a Suspected AM

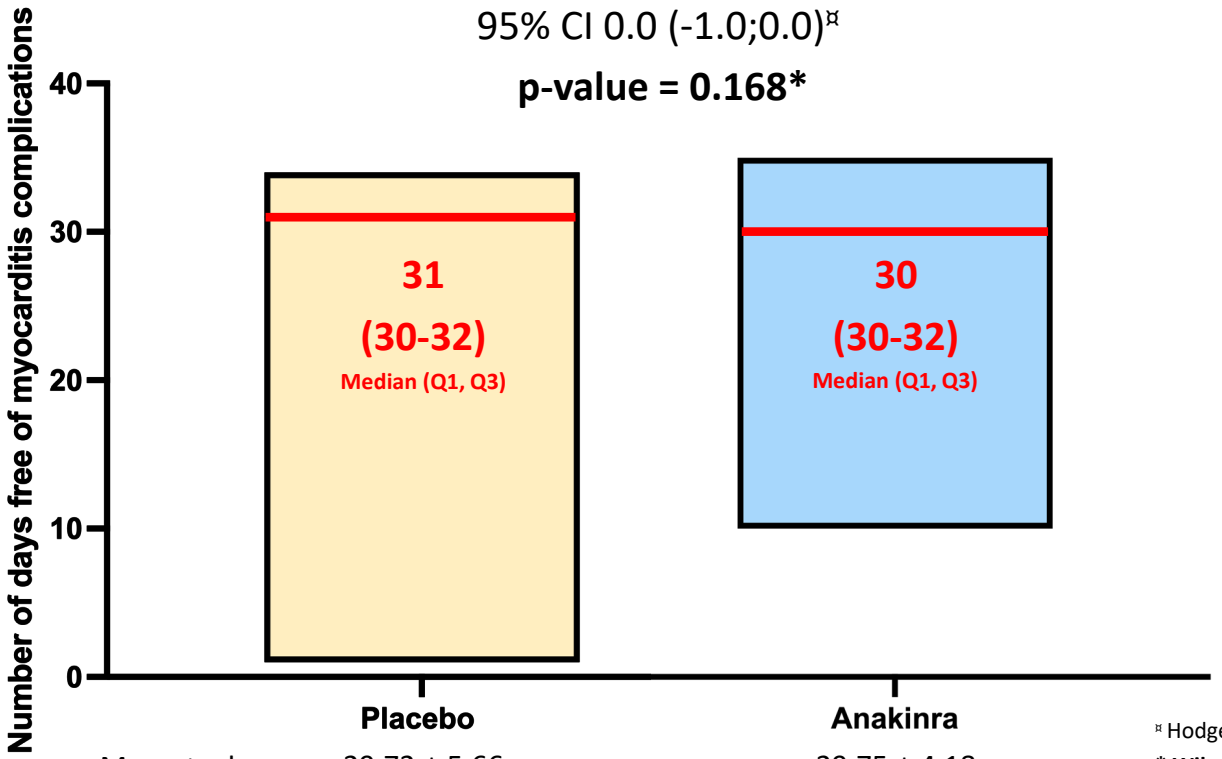
Confirmation of diagnosis and randomization

Hospital Discharge

Primary Endpoint

Number of days considered for the Primary Endpoint

Primary Endpoint : Number of days free of complications



Red Line = Median

Box = Min-Max

¤ Hodges-Lehmann's median difference

*** Wilcoxon-Mann Whitney test**

Non parametric Ancova p-value = 0.192

Components of the Primary endpoint

	Anakinra N=57	Placebo N=60	Odds Ratio (95% CI)
Composite outcome* — no. (%)	**6 (10.5%)**	**10 (16.7%)**	**0.59 (0.19; 1.78)**
Ventricular arrhythmia at 28 days post discharge — no. (%)	1 (1.8%)	1 (1.7%)	
Chest pain requiring medication at 28 days post discharge — no. (%)	**2 (3.5%)**	**6 (10.0%)**	**0.33 (0.06; 1.76)**
Ventricular dysfunction (LVEF<50%) at 28 days post discharge — no. (%)	4 (8.5%)	4 (7.4%)	1.16 (0.27; 5.09)

***ventricular arrhythmia, HF, chest pain requiring medication or LVEF<50% at 28 days post discharge — no. (%)**

Safety Endpoints

	Anakinra N=58	Placebo N=59	Odds Ratio* (95% CI)	Odds Ratio** (95% CI)
Serious Adverse Event — no. of patients (%)	7 (12.1%)	6 (10.2%)	1.21 (0.37; 3.94)	1.20 (0.35; 4.07)

	Anakinra	Placebo
Serious Adverse Event*. — no. of events *One patient can present several events*	10/10	6/6
Serious Adverse Event potentially related to the drug . ***(Hepatic cytolysis, n=1)***	1	0
Severe Infection	0	0

* Unadjusted Odds Ratio. **Adjusted Odds Ratio for Age and baseline LVEF

Conclusions

ARAMIS, the largest RCT in acute myocarditis, enrolled for the first time an all-comer **acute** myocarditis population diagnosed on **CMR**, mostly at **low risk of events.**

A short administration of anakinra did **not increase the number of days free of myocarditis complications**

There was no safety issue with anakinra administered during the acute phase of myocarditis diagnosed without EMB (**no proof of absence of viral replication**)

Further RCT studies are needed to explore the potential benefit of the anti-inflammatory strategy in acute myocarditis patients at **higher risk of events**

Larger studies are needed to evaluate **prolonged anti inflammatory strategies** in acute myocarditis patients at « low-to-moderate risk » (16% of events at M1)

Thank You to the ARAMIS Team

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