NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von: Deutsches Krebsforschungszentrum Universitätsklinikum Heidelberg Thoraxklinik-Heidelberg Deutsche Krebshilfe

Study Title:

A randomized, placebo-controlled, phase IIIb HPV vaccination trial with Gardasil®/ Gardasil®9 in patients with recurrent condylomata acuminata (GaReCo-Study)

Short Title/ Acronym: GaReCo-trial

In this multicenter, national study male and female patients with recurrent condylomata acuminata received vaccination with either Gardasil®/ Gardasil®9 or placebo (NaCl solution) at month 0, 2, and 6. Endpoint of the trial was recurrence of condylomata acuminata within 6 months after the third vaccination.

Final Study Report according to §42b AMG and §13(9) GCP-V

Version Number/ Date:	Final 01, May 13th 2020
Investigational Product:	Gardasil®/ Gardasil®9
EudraCT Number:	2012-004007-13
Protocol-Number:	NCT-2010-1090, 1.7 August 9th 2017

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Study Initiation and Completion Dates:
First Patient in: April 29th 2014
Last patient in: May 8th 2018
Date of early study termination: May 21st 2019
Last Patient Last Visit: May 21st 2019
Data base lock: April 8th 2020

Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Sponsor / or Designated Representatives	M. Pawlita	Heidelberg, 13.5.20
	Dr. med. Michael Pawlita Name, Title	Place, Date
Principal or Coordinating Investigator	Prof. Dr. med. Joachim Rom Name, Title	Place, Date
Biostatistician	Lisa-Marie Rother, M.Sc. Name, Title	Place, Date

Signatures

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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Sponsor / or Designated Representatives	Dr. med. Michael Pawlita Name, Title	Place, Date
Principal or Coordinating Investigator	Prof. Dr. med. Joachim Rom Name, Title	Frankfurt, 13.05.2020 Place, Date
Biostatistician	Lisa-Marie Rother, M.Sc. Name, Title	Place, Date

Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Sponsor / or Designated Representatives	Dr. med. Michael Pawlita	
	Name, Title	Place, Date
Principal or Coordinating Investigator	Prof. Dr. med. Joachim Rom	
	Name, Title	Place, Date
Biostatistician	Rother Lisa-Marie Rother, M.Sc.	Weinheim, 18.05.2020
	Name, Title	Place, Date

Name of Sponsor/Company:

Deutsches Krebsforschungszentrum (DKFZ) Heidelberg

Im Neuenheimer Feld 280

69120 Heidelberg

Name of Finished Product:

Gardasil®/ Gardasil®9

Name of Active Ingredient:

Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant (Gardasil®)

Human Papillomavirus 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Vaccine, Recombinant (Gardasil®9)

Title of Study:

A randomized, placebo-controlled, phase IIIb HPV vaccination trial with Gardasil®/ Gardasil®9 in patients with recurrent condylomata acuminata (GaReCo-Study)

Short Title/ Acronym:

GaReCo

Protocol versions:

Final 1.2, July 11th 2013 (First authorization)

Final 1.3, October 2nd 2013 (Substantial Amendment 1)

Final 1.4, May 26th 2014 (Substantial Amendment 4)

Final 1.6, January 10th 2017 (Substantial Amendment 10)

Final 1.7, August 9th 2017 (Substantial Amendment 12)

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Publication (reference):

-

Studied period (years):

Date of first enrollment: April 29th 2014

Interruption (of recruitment): January 5th 2017 – February 7th 2017

Date of last enrollment: May 8th 2018

Date of early trial termination: May 21st 2019

Date of last completed: May 21st 2019

Early termination after the treatment of 86 patients due to substantial delay of the recruitment.

Phase of development:

Phase IIIb

Objectives:

The *Primary Objective* of this trial was to evaluate the efficacy of Gardasil®/ Gardasil®9 compared with placebo on the prevention of recurrence of condylomata acuminata.

Secondary Objectives:

To compare Gardasil®/ Gardasil®9 versus placebo with respect to:

- Time to recurrence of condylomata acuminata from the day of administration of first vaccination up to 6 months after last vaccination
- Incidence of HPV6/11-related external condylomata acuminata*
- Presence (DNA) and biological activity (RNA) of HPV6/11 and other HPV types in condylomata acuminata at visit 1 to visit 4*
- HPV-specific immunological outcomes (HPV antibody at visit 1 to visit 4 and T-cell responses at visit 1, visit 3 and visit 4)*
- Associations between immunological and clinical outcomes*
- Safety and tolerability

Please note:

Due to unavailable data concerning immunological outcomes at time of preparation of this report, the secondary objectives marked with * could not be analyzed.

Methodology:

Phase IIIb, randomized, placebo-controlled, blinded, multicenter, parallel, two-arm study. Upon meeting eligibility criteria, patients were randomized (1:1) to one of the two following treatment arms: Gardasil®/ Gardasil®9 or placebo. Patients, who were randomized to the placebo group, were offered to receive Gardasil®/ Gardasil®9 at their last study visit (visit 4, month 12) outside the trial protocol.

Visit schedule:

- Screening: Day -14 to day 0
- Visit 1/ First vaccination: Month 0
- Visit 2/ Second vaccination: Month 2 (± 4 weeks)
- Visit 3/ Third vaccination: Month 6 (± 8 weeks)
- Visit 4: Month 12 (± 4 weeks)

Number of patients (planned and analyzed):

Number of patients planned: 200

Number of patients analyzed: 86

Diagnosis and main criteria for inclusion:

External condylomata acuminata (at least one) defined as: condylomata acuminata, condylomata gigantea, keratotic genital warts, papular warty-like lesions within 6 months after removal of previously clinically diagnosed external condylomata acuminata (at least one).

Investigational product, dose and mode of administration, batch number:

Drug Code: *Gardasil® and Gardasil®9*, ATC Code: J07BM01 and J07BM03

International Nonproprietary Name (INN): Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant and Human Papillomavirus 9-valent (Types 6, 11, 16, 18, 31, 33, 45 ,52, 58) Vaccine, Recombinant

Pharmaceutical formulation: injection

Route of administration: i.m.

Storage conditions: 2-8°C

Manufacturer/Importer: Sanofi Pasteur MSD (since January 1st 2017: MSD)

Marketing Authorisation number: EU/1/06/357/003 and EU/1/15/1007/001

Dose: 0,5 ml at month 0, 2, 6 (in total: 1,5 ml)

Batch numbers: *Gardasil®:* J006288, J011660, J015438, J016199, K001351, K002845, K004216, K008948, K011297, K014311, K014988, K023251, L003897, L005502, L017859, L035405, L038424, L044836, L046836, M015594, M025706, M026288, R016446, R020515 and *Gardasil®9:* M048598, N020454, N032782, R001115

Reference therapy, dose and mode of administration, batch number:

Drug Code: Isotonic saline 0.9%, ATC Code: None

International Nonproprietary Name (INN): Physiological NaCl solution

Pharmceutical formulation: injection

Route of administration: i.m.

Storage conditions: none

Manufacturer/Importer: Eifelfango® Chemisch Pharmazeutische Werke

Dose: 0,5 ml at month 0, 2, 6 (in total: 1,5 ml)

Batch numbers: 3141, 5124, 5242, 7198-2

Duration of treatment:

Three vaccinations at months 0, 2 and 6 leading to a treatment duration of 6 months.

Criteria for evaluation:

Efficacy:

The *primary efficacy endpoint* is the recurrence of condylomata acuminata within 6 months after the third vaccination.

Recurrence was initially defined as (1) the presence of new lesion(s) in the area which had been treated or within 1 cm near the previously treated area and/or (2) appearance of new warts/lesions on other genital sites. All recurrences are verified by biopsy and histology.

Due to unavailable data on histological verification at the time of preparation of this report, a new definition of recurrence is introduced in the Statistical Analysis Plan:

Clinical recurrence=yes, if (1) patient has at least one recurrent or new lesion at visit 4 (scheduled 6 months after the third vaccination), which was (2) ablated before (in case of a recurrent lesion) and (3) has been confirmed by the clinician (CRF documentation signed by investigator).

Otherwise, Recurrence=No

Secondary Efficacy Endpoints:

- Time to recurrence of condylomata acuminata from the day of administration of first vaccination up to 6 months after last vaccination
- Incidence of HPV6/11 related external condylomata acuminata*
- Presence (DNA) and biological activity (RNA) of HPV6/11 and other HPV types in condylomata acuminata at visit 1 to visit 4*
- HPV specific immunological outcomes (HPV antibody at visit 1 to visit 4 and T-cell responses at visit 1, visit 3 and visit 4)*
- Associations between immunological and clinical outcomes*

Please note:
Due to unavailable data concerning immunological outcomes at the time of preparation of this report, the secondary endpoints marked with * could not be analyzed.

Safety:
Type, intensity, seriousness and relatedness of adverse events occurring or worsening after the start of the first study treatment.

Statistical methods:

Statistical analysis:

The GaReCo-trial was stopped prematurely when 86 patients were treated due to slow recruitment. For this reason, any confirmatory statistical analysis was inappropriate. The statistical analysis actually performed was therefore in a strictly exploratory and mainly descriptive manner. All data collected which have value towards assessing the safety, efficacy or other properties of the drug are reported in either the summary presentations or listings or in both.

Exploratory analysis of the efficacy endpoints:

- For the primary endpoint, the number of recurrences in the Gardasil®/ Gardasil®9 and placebo group was determined for all patients in the Full Analyis Set and Per Protocol Set. These information were only presented in descriptive tables. Due to the highly reduced sample size, statistical testing was inappropriate and thus no statistical test for differences was performed
- As the secondary endpoint, time-to-recurrence was determined for every patient in the Full Analysis Set. The Kaplan-Meier estimates were used to compute the proportion of patients not experiencing a recurrence with the 95% CI, calculated using Greenwood's formula. The treatment group effect was estimated using the log-rank test. The hazard ratio and the corresponding 95% CI were estimated by proportional Hazards regression.
- The response variable recurrence (yes/no) was further explored using a logistic regression model to investigate the effect of the covariates of interest on the recurrence rate. Variables included were: treatment, study center, age, gender, smoking status, country of birth and number of sexual partners in the last 12 months. Odds ratios with exact 95% CI were used as a measure of association between the covariates and recurrence.

Please note, that the secondary analyses were originally planned to be conducted using the Per Protocol Set, but due to a high amount of major protocol deviations, the Full Analysis Set was used instead as suggested in the Statistical Analysis Plan. The Statistical Analysis Plan also stated that the switch from Gardasil® to Gardasil®9 could introduce bias into the

results and a test for differences may be performed, but due to the early trial termination (only 4 patients received Gardasil®9 according to the drug account) a test on differences was deemed inappropriate.

Analysis of the safety data:

Adverse Events (AE) were coded with the MedDRA dictionary version 22.0. Frequencies of patients experiencing at least one AE were displayed. Detailed information collected for each AE included: A description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Summaries of incidence rates (frequencies and percentages) of AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) were prepared. Such summaries were displayed for all AEs, AEs by intensity and AEs by relationship to study drug. Summary tables present the number of patients observed with AEs, the corresponding percentages, and exact 95% two-sided Clopper-Pearson CI.

Study Population

A total of 86 patients were randomized and treated at 10 investigational centers in Germany and randomized to be treated with Gardasil®/ Gardasil®9 (n=45, 1 did not receive any trial medication) or placebo (n=42). Seventy-one patients (83%) completed the study 6 months after the last vaccination. The percentage of patients with premature study termination was higher in the placebo group (21%) than in the Gardasil® group (14%). Due to a high amount of major protocol deviations, only 50% of the patients could be analyzed as 'per protocol'. Despite randomization, the treatment groups were slightly inhomogeneous at baseline with regard to smoking status and sexual partners in the last 12 months. The percentage of patients from the Full Analysis Set who are also part of the Per Protocol Set was higher in the Gardasil® group (57%) than in the placebo group (43%). For details on discontinuations, analysis populations and demographics of patients, see the following tables:

Discontinuations from Study:

		Placebo N (%)	**Gardasil®/ Gardasil®9 N (%)**
Status at the End of the Study	All	42 (100.0)	44 (100.0)
	Patient completed study 6 months after last vaccination*	33 (78.6)	38 (86.4)
	Premature study termination	9 (21.4)	6 (13.6)
Reason for Premature Study Termination**	Lost to follow-up	4 (44.4)	5 (83.3)
	(Serious) Adverse Event	1 (11.1)	0
	Protocol violation	0	1 (16.7)
	Withdrawal of informed consent	3 (33.3)	0
	Death	0	0
	Pregnancy	1 (11.1)	0
	Investigators decision	0	0
	Other reasons	1(11.1)	1 (16.7)

* For one patient no information was ticked in the CRF, but this patient received all vaccinations and also attended visit 4, so for this table, the patient was sorted in this group to give a better overview of the available information.

** Multiple answers were possible.

Analysis Populations:

	Placebo, n (%)	Gardasil®/ Gardasil®9, n (%)	All Patients, n (%)
Full Analysis Set/ Safety Set	42 (100.0)	44 (100.0)	86 (100.0)
Per Protocol Set	18 (42.9)	25 (56.8)	43 (50.0)

Demographics:

	Placebo	Gardasil®/ Gardasil®9
All patients, n (%)	42 (100.0)	44 (100.0)
Age continuous (years), Mean (SD)	34.7 (9.9)	34.3 (10.4)
Age categorical (years), n (%)		
18-44	34 (81.0)	36 (81.8)
45-64	8 (19.0)	7 (15.9)
≥65	0	1 (2.3)
Gender, n (%)		
Female:	11 (26.2)	11 (25.0)
Male:	31 (73.8)	33 (75.0)
Smoking status, n (%)		
Smoker:	16 (38.1)	20 (45.5)
Non-smoker:	23 (54.8)	19 (43.2)
Ex-smoker:	3 (7.1)	4 (9.1)
Missing:	0	1 (2.3)
Sexual partners in the last 12 months, n (%)		
0	3 (7.1)	1 (2.3)
1	24 (57.1)	26 (59.1)
2 - 4	11 (26.2)	9 (20.5)
More than 4	2 (4.8)	5 (11.4)
Answer refused	2 (4.8)	2 (4.5)
Missing	0	1 (2.3)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

This randomized controlled study was performed in order to evaluate the effects of Gardasil®/ Gardasil®9 versus placebo treatment on recurrence of condylomata acuminata. The primary endpoint of the study was recurrence within 6 months after the third vaccination. The secondary endpoint analyzed was Time-to-recurrence. Additionally a logistic regression model was fitted with the response variable 'recurrence' using different demographic covariates. The stipulated working hypothesis was superiority of Gardasil®/ Gardasil®9 compared to placebo with respect to recurrence.

The number of recurrences per treatment arm is shown in the following table for the Full Analysis Set:

Recurrence	Placebo, n (%)	Gardasil®/ Gardasil®9, n (%)
Yes	11 (26.2)	12 (27.3)
No	31 (73.8)	32 (72.7)

Due to the strongly reduced sample size and the correspondingly reduced power, any confirmatory statistical analysis was inappropriate and thus no statistical test was performed to evaluate the primary endpoint. According to the table above, the results in both groups are similar: Most patients had no recurrence within 6 months after the third vaccination (74% in the placebo group and 73% in the Gardasil® group).

For the results in the Per Protocol Set, see the following table:

Recurrence	Placebo, n (%)	Gardasil®/ Gardasil®9, n (%)
Yes	3 (16.7)	8 (32.0)
No	15 (83.3)	17 (68.0)

In the Per Protocol Set the number of patients in the placebo group is lower than in the Gardasil® group (18 vs. 25). As for the Full Analysis Set, most patients had no recurrence within 6 months after the third vaccination (83% in the placebo group and 68% in the Gardasil® group).

The secondary endpoint Time-to-recurrence is analyzed using the Full Analysis Set. Please note, that for this endpoint the time to recurrence of condylomata acuminata from the day of administration of the first vaccination up to 6 months after the last vaccination is taken. Thus the number of recurrences for this endpoint differs to the number of recurrences for the primary endpoint which only considered a recurrence that appeared within 6 months after the third vaccination.

The number of patients with the event were similar in the two groups (64% (28/44) in the Gardasil® group and 64% (27/42) in the placebo group). The hazard ratio with 95% confidence limits estimated by proportional hazard regression was 1.133 (0.663, 1.937) meaning that the risk of recurrence is 13% higher in the placebo group as compared to the Gardasil® group, showing a slight non-significant superiority of the Gardasil® group.

A logistic regression was performed using backward elimination, reference coding and a significance level of 0.35 for removing effects. The full model contained age, study center, treatment, country of birth, number of sexual partners in the last 12 months, gender and smoking status. The effects country, smoking status, treatment and study center were sequentially removed from the model in this order. The final effects in the model were age, number of sexual partners (reference: 0) and gender (reference: female) with the following odds ratio estimates:

Effect	Odds Ratio Estimate	Lower/Upper 95% CI
Age	1.04	(0.99, 1.10)
Partners		
1 vs 0	0.05	(0.003, 0.67)
2-4 vs 0	0.03	(0.002, 0.57)
Answer refused vs 0	0.03	(<0.001, 1.007)
More than 4 vs 0	0.06	(0.003, 1.17)
Sex		
Male vs female	5.82	(1.13, 29.9)

For the available data, the chance of recurrence within 6 months after the third vaccination increased with age. Male patients and patients with 0 sexual partners in the last 12 months had a higher chance of being recurrent compared to female patients and patients with at least one sexual partner in the last 12 months (and patients who refused to reply the answer about number of sexual partners). These information only describe the underlying data and shall not serve as a prediction model.

SAFETY RESULTS:

Overall 26/86 (30%) patients experienced at least one (all causality) AE. The incidence of AEs was slightly lower in the placebo group (29% (12/42 patients)), than in the Gardasil® group (32% (14/44 patients)). The most frequent AE in terms of system organ class was "Injections and infestations". AEs with causality assessed as definitely, probably, possibly related or with missing information on relatedness were considered as treatment related. 1 patient (2%) in the placebo group and 6 patients (14%) in the Gardasil® group experienced at least one treatment related AE. For more information see the following table:

Adverse Events:

	Placebo, n (%)	Gardasil®/ Gardasil®9, n (%)
Overview all AEs		
Any AE	12 (28.6)	14 (31.8)
Any SAE	2 (4.8)	2 (4.5)
Any Severe Adverse Event (Severity=severe)	2 (4.8)	2 (4.5)
Overview related AEs*		
Any AE	1 (2.4)	6 (13.6)
Any SAE	0	1 (2.3)
Any Severe Adverse Event (Severity=severe)	0	0
AEs by System Organ Class (MedDRA 22.0), all causalities		
Blood and lymphatic system disorders	0	1 (2.3)
Gastrointestinal disorders	1 (2.4)	2 (4.5)
General disorders and administration site conditions	3 (7.1)	4 (9.1)
Infections and infestations	7 (16.7)	8 (18.2)
Injury, poisoning and procedural complications	3 (7.1)	2 (4.5)
Musculoskeletal and connective tissue disorders	0	1 (2.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (4.8)	0
Nervous system disorders	1 (2.4)	2 (4.5)
Psychiatric disorders	1 (2.4)	0
Renal and urinary disorders	0	1 (2.3)
Reproductive system and breast disorders	1 (2.4)	2 (4.5)
Skin and subcutaneous tissue disorders	1 (2.4)	3 (6.8)
Surgical and medical procedures	0	1 (2.3)

*AEs with causality assessed as definitely , probably, possibly related or missing were considered

One patient who was part of the Gardasil® group experienced two AEs (injection reactions) within 30 minutes after the third vaccination: tiredness and dizziness. All other patients experienced no injection reactions.

One patient, who was part of the placebo group, terminated the study early after one vaccination, and thus did not receive any further study medication. Pregnancy was given as reason for early termination in the CRF. According to the DSUR No. 3, the patient was

included in the study on July 5th 2016 and the first application of study medication was done on the same day (visit 1). She did not appear to visit 2, so she dropped out. On November 1st 2016 she came to the outpatient department due to recurrence of the underlying disease and reported that she is pregnant (18th week of pregnancy). Therefore the blind was broken for this patient. Due to the fact that she was in the placebo group, an expedited reporting was not carried out after consultation with the national competent authority (PEI).

CONCLUSION:

Due to the early study termination resulting in reduced sample size and correspondingly reduced power any conclusions in regard to study objectives could not be demonstrated. Based on the data of the 86 patients, there were no relevant group differences with respect to the efficacy results. Overall, the safety profile of the Gardasil® group was slightly inferior as compared to the placebo group.

Please note, that due to unavailable data on immunological outcomes at the time of preparation of this report, it was not possible to double-check if the patients received the treatment that they were assigned to and that patients in the placebo group were not vaccinated outside the trial, thus the explanatory power of these results might be reduced.

Substantial amendments / interruptions or early termination:

Substantial amendments:

IEC Independent Ethics Committee(s)

Amendment No.	Content	Approval Date
01	Change of LKP (V 1.3)	February 11th 2014
02	Change of PI and additional site	February 11th 2014/ 14th 2014
03	Additional site	May 20th 2014
04	Protocol amendment (V 1.4)	July 15th 2014
05	Change of deputy PI	June 26th 2015
06	Change of deputy PI	August 21st 2015
07	Additional site	February 2nd 2016
08	Additional site	October 20th 2016
09	Change of PI and deputy PI	November 28th 2016
10	Change of LKP, protocol amendment (V 1.6)	January 31st 2017
12	Switch to Gardasil®9 (V 1.7)	October 12th 2017
13	Change of deputy PI	November 29th 2017
14	Change of PI	February 5th 2018
15	Change of deputy PI	April 3rd 2019

Paul Ehrlich Institute (PEI)

Amendment No.	Content	Approval Date
01 + 02	Change of LKP (V 1.3)	February 28th 2014
04	Protocol amendment (V 1.4)	July 11th 2014
10	Change of LKP, protocol amendment (V 1.6)	January 5th 2017
11	Continuation of recruitment	February 7th 2017
12	Switch to Gardasil®9 (V 1.7)	October 10th 2017

Interruptions:

At the request of the ethics committee Heidelberg, the recruitment was suspended from January 05th 2017 until February 07th 2017 for formal reasons until the approval of the coordinating investigator change submitted in December 2016 (new CI (LKP): Dr. Rom, Heidelberg). With this change of CI and the wish of the ethics committee LAGeSo Berlin to give up the lead management, a re-evaluation of the study at the ethics committee Heidelberg became necessary.

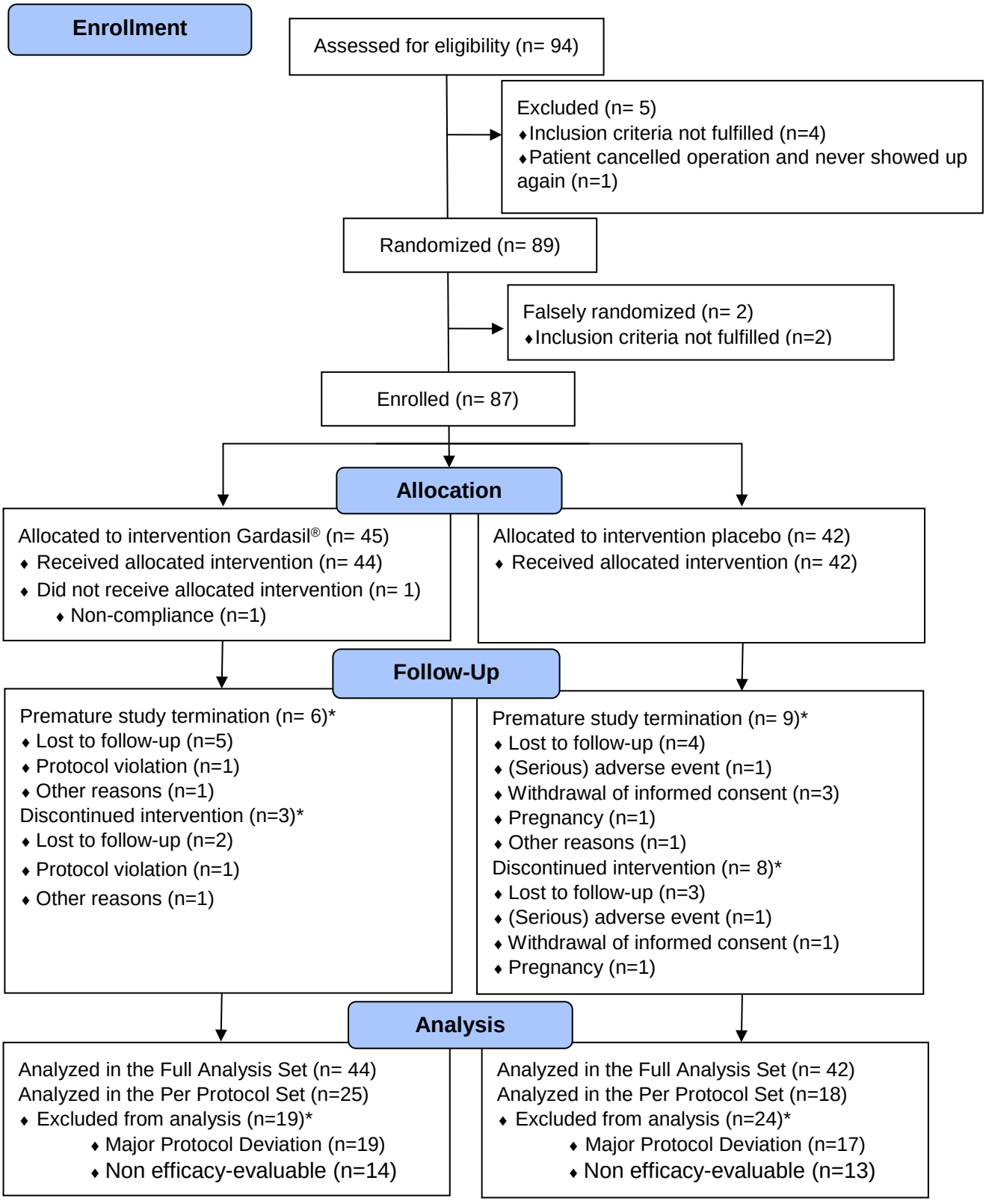
Early Study termination:

Due to a poor recruitment rate enrollment of new patients was stopped after the treatment of 86 out of 200 planned patients. The last patient-last visit was on May 21st 2019.

Date of the report:

May 13th 2020

CONSORT 2010 Flow Diagram



*Multiple reasons for the same patient were possible