Data Analysis: Rituximab Maintenance Treatment for ME/CFS

An Open-Label Phase II Study

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PLOS ONE

RESEARCH ARTICLE

B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment

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ME/CFS

or **Myalgic Encephalopathy/Chronic Fatigue Syndrome** is a disease commonly characterized by *severe fatigue*, *cognitive disturbances*, *pain*, *sleep problems*, *sensory hypersensitivity* and *post-exertional malaise*, as well as several symptoms related to immune and autonomic function.

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Effect on Quality of Life: Patients with severe ME/CFS suffer major functional impairments and often a range of debilitating symptoms. The disease carries high socioeconomic costs.

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Effect on Quality of Life: Patients with severe ME/CFS suffer major functional impairments and often a range of debilitating symptoms. The disease carries high socioeconomic costs.

Causes and Treatment: The causes of ME/CFS are unknown. Hence no standard drug treatment has been established.

Previous trials

Pilot study: - 3 patients

- clinical activity for B-cell depletion using rituximab

Phase II trial: - 30 patients

- randomized, double-blind and placebo-controlled
- no difference between the rituximab and placebo groups
- significant difference in favor of the rituximab group in the course of *Fatigue score* during follow-up
- ME/CFS could be a variant of an autoimmune disease

Overview

The **primary endpoint** was effect on self-reported ME/CFS symptoms during follow-up.

Secondary endpoints were effects on the ME/CFS symptoms at 3, 6, 10, 15, 20, 24, 30 and 36 months assessed by the SF-36 questionnaire, the longest consecutive response period, the fraction of included patients still in response at end of study and toxicity during follow-up

Type of Analysis

Intention to treat

Study Design

- one-armed
- open-label
- Single center

Sample Size

29 patients

Primary Endpoint

efficacy endpoint

Follow-ups

at 3, 6, 10, 15, 20, 24, 30 and 36 months

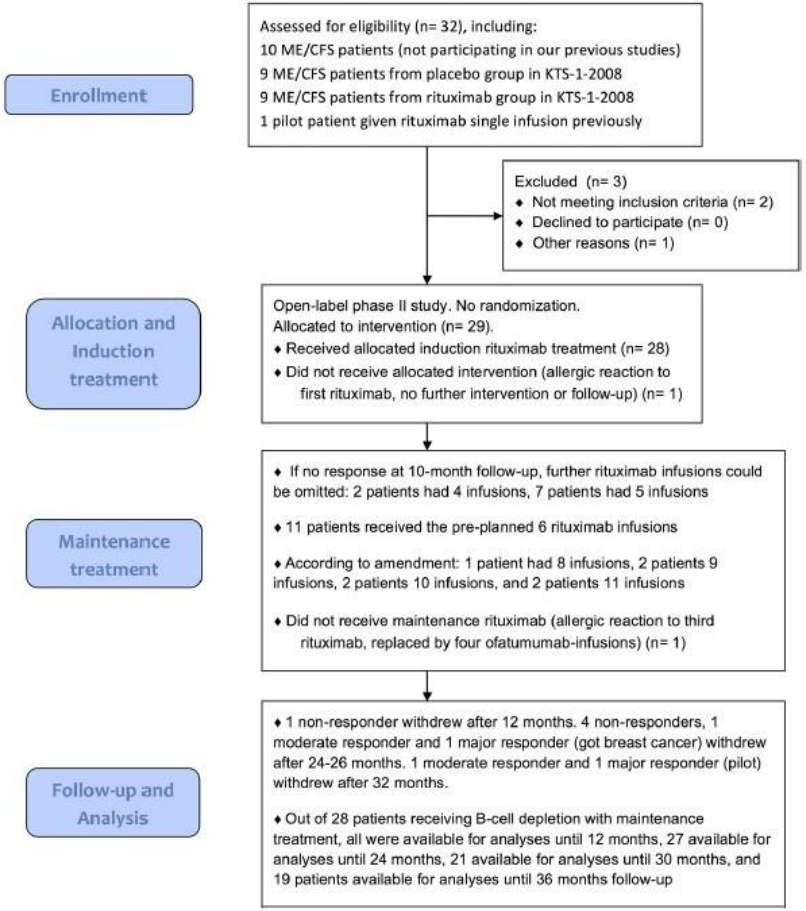
Target Population

Inclusion criteria

- ★ diagnosis of ME/CFS according to the Fukuda 1994 criteria
- ★ 18–66 years of age

Exclusion criteria

- ❑ not meeting the diagnostic criteria for ME/CFS
- ❑ pregnancy/lactation
- ❑ previous malignant disease
- ❑ previous severe immune system disease (except autoimmune)
- ❑ previous long-term systemic immunosuppressive treatment
- ❑ endogenous depression
- ❑ lack of ability to adhere to protocol


Enrollment
Assessed for eligibility (n= 32), including:
10 ME/CFS patients (not participating in our previous studies)
9 ME/CFS patients from placebo group in KTS-1-2008
9 ME/CFS patients from rituximab group in KTS-1-2008
1 pilot patient given rituximab single infusion previously
Excluded (n= 3)
Not meeting inclusion criteria (n= 2)
Declined to participate (n= 0)
Other reasons (n= 1)
Allocation and Induction treatment
Open-label phase II study. No randomization.
Allocated to intervention (n= 29).
Received allocated induction rituximab treatment (n= 28)
Did not receive allocated intervention (allergic reaction to first rituximab, no further intervention or follow-up) (n= 1)
Maintenance treatment
If no response at 10-month follow-up, further rituximab infusions could be omitted: 2 patients had 4 infusions, 7 patients had 5 infusions
11 patients received the pre-planned 6 rituximab infusions
According to amendment: 1 patient had 8 infusions, 2 patients 9 infusions, 2 patients 10 infusions, and 2 patients 11 infusions
Did not receive maintenance rituximab (allergic reaction to third rituximab, replaced by four ofatumumab-infusions) (n= 1)
Follow-up and Analysis
1 non-responder withdrew after 12 months. 4 non-responders, 1 moderate responder and 1 major responder (got breast cancer) withdrew after 24-26 months. 1 moderate responder and 1 major responder (pilot) withdrew after 32 months.
Out of 28 patients receiving B-cell depletion with maintenance treatment, all were available for analyses until 12 months, 27 available for analyses until 24 months, 21 available for analyses until 30 months, and 19 patients available for analyses until 36 months follow-up

Author conclusions

- **Lasting improvements** in self-reported Fatigue score, were detected in 18 out of 29 patients (intention to treat).

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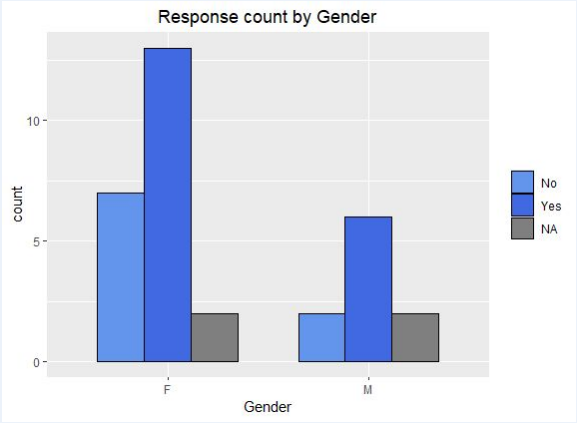
- After 36 months 11 out of 18 responding patients were still in ongoing clinical remission.
- For major responders, the **mean lag time** from first rituximab infusion until start of clinical response was **23 weeks** (range 8–66).

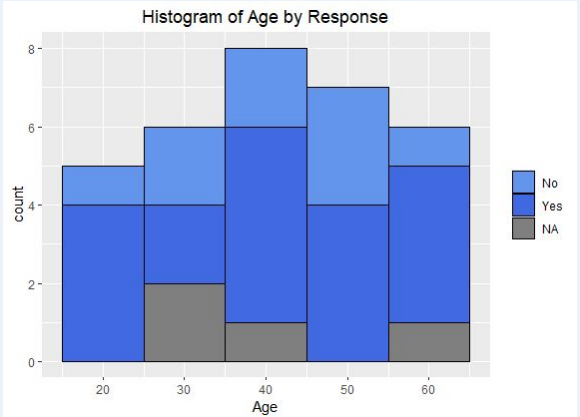
Our Analysis

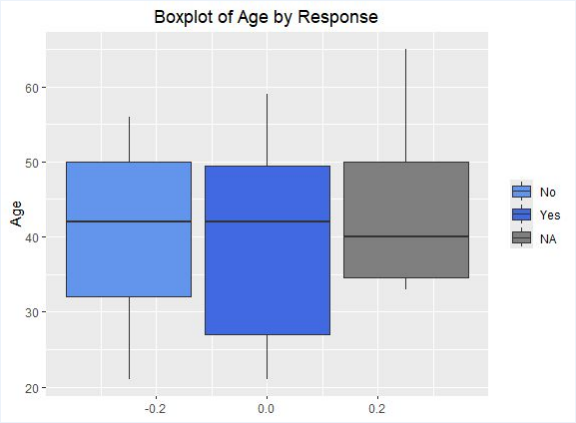
Age and gender

- no significant difference in response proportion between genders
- respondents and non-respondents were of similar age

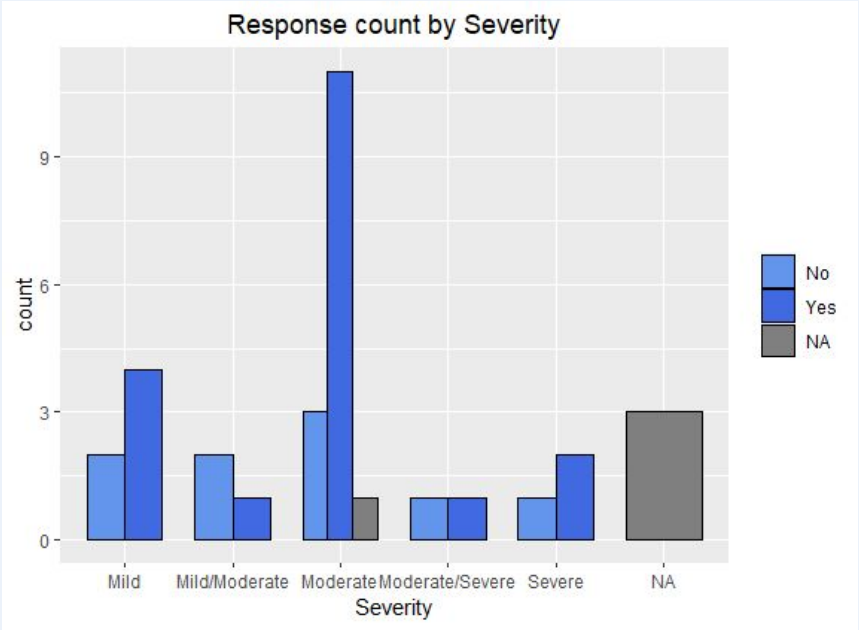
	0 (N=9)	1 (N=19)	Overall (N=28)
Age			
Mean (SD)	40.4 (12.2)	40.5 (12.8)	40.5 (12.4)
Median [Min, Max]	42.0 [21.0, 56.0]	42.0 [21.0, 59.0]	42.0 [21.0, 59.0]
Gender			
F	7 (77.8%)	13 (68.4%)	20 (71.4%)
M	2 (22.2%)	6 (31.6%)	8 (28.6%)

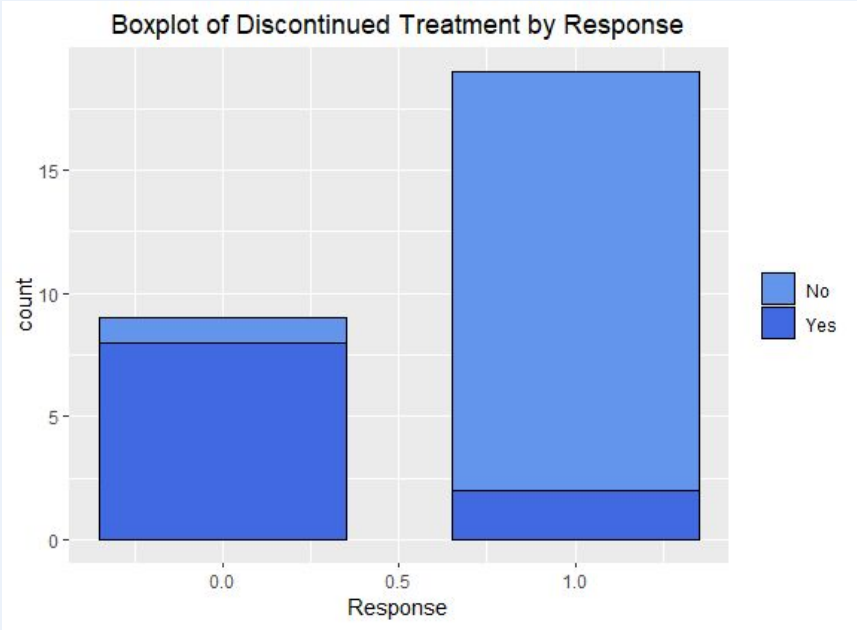


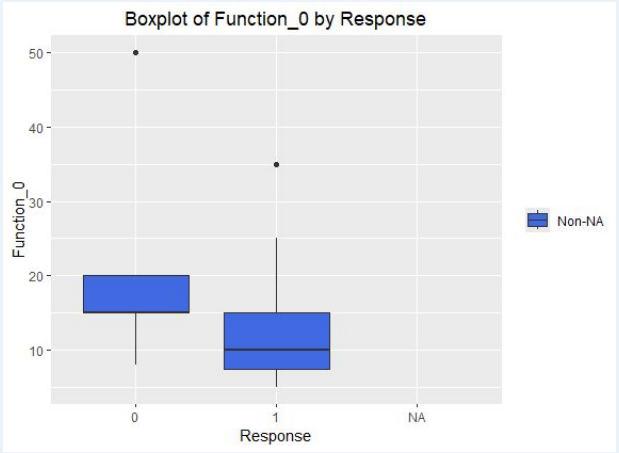


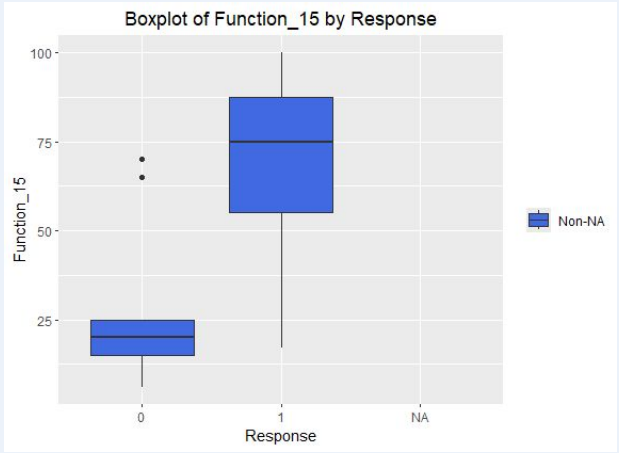


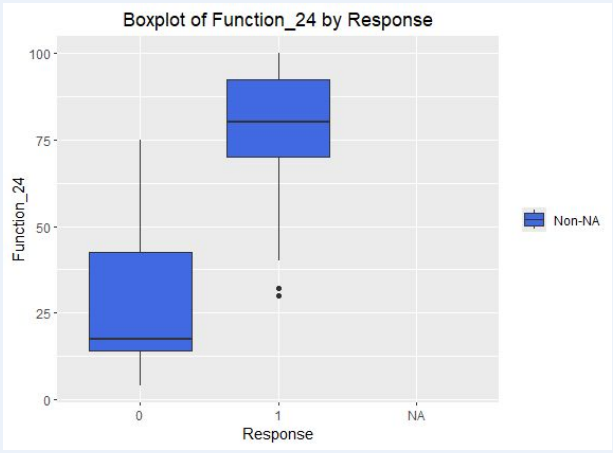
Severity and Discontinued Treatment






Boxplot of Function_0 by Response
Function_0
50
40
30
20
10
0
1
NA
Response
Non-NA


Boxplot of Function_15 by Response
Function_15
100
75
50
25
0
1
NA
Response
Non-NA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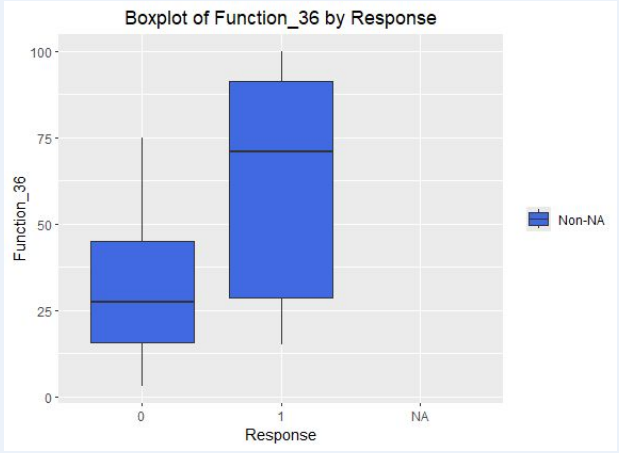
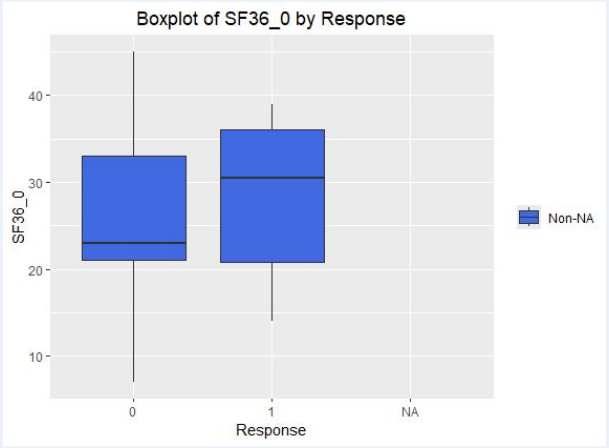
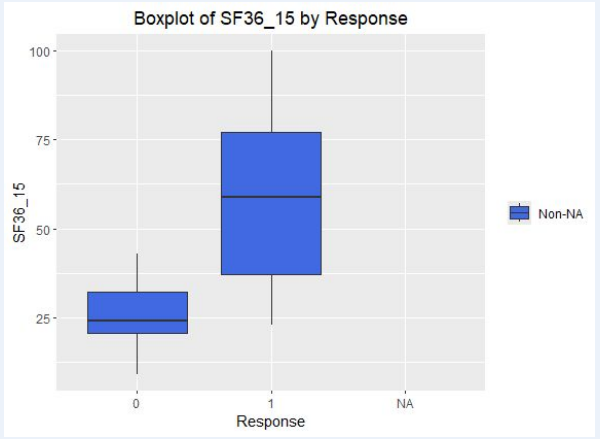
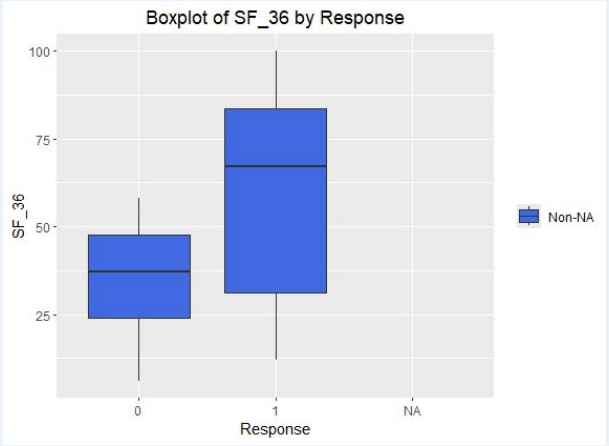
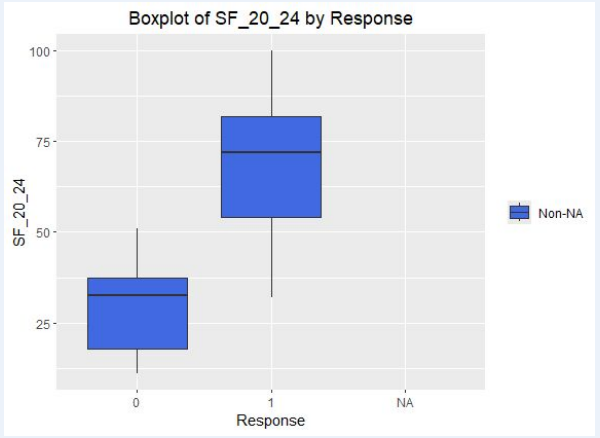
Function_24
100
75
50
25
0
1
NA
Response
Non-NA


Boxplot of Function_36 by Response
Function_36
100
75
50
25
0
1
NA
Response
Non-NA


Boxplot of SF36_0 by Response
SF36_0
40
30
20
10
0
1
NA
Response
Non-NA


Boxplot of SF36_15 by Response
SF36_15
100
75
50
25
0
1
NA
Response
Non-NA


Boxplot of SF_36 by Response
SF_36
100
75
50
25
0
1
NA
Response
Non-NA


Boxplot of SF_20_24 by Response
SF_20_24
100
75
50
25
0
1
NA
Response
Non-NA

Modelling factor significance

- We used logistic LASSO regression to model whether response occurred.
- We used data of all patients who began treatment.

	s0
(Intercept)	-2.951209e-01
GenderF	.
GenderM	.
Age	.
Discontinued_TreatmentNo	2.053714e+00
Discontinued_TreatmentYes	-8.367267e-15
Infection_triggerNo	.
Infection_triggerPossible	.
Infection_triggerYes	.
InfectionAirways	.
InfectionBorellia	.
InfectionGI	.
InfectionMono	.
InfectionPneum	.
InfectionThroat	.
InfectionViral	.
Disease_duration	.
SeverityMild	.
SeverityMild/Moderate	.
SeverityModerate	.
SeverityModerate/Severe	.
SeveritySevere	.
Family_ADNo	.
Family_ADYes	.
SF36_0	.
SF36_15	.
SF_20_24	.
SF_36	.
Function_0	-1.579768e-02
Function_15	.
Function_24	7.064396e-01
Function_36	.

Additional model

We used linear LASSO regression to model duration of the response.

	s0
(Intercept)	3.243101e+01
GenderF	2.941961e-01
GenderM	-1.065711e-14
Age	-2.541371e+00
Discontinued_TreatmentNo	4.836201e+01
Discontinued_TreatmentYes	-8.902051e-15
Infection_triggerNo	.
Infection_triggerPossible	2.918157e+01
Infection_triggerYes	-8.788185e+00
InfectionAirways	2.845218e+01
InfectionBorellia	-2.140066e+01
InfectionGI	-1.901563e+01
InfectionMono	1.037984e+01
InfectionPneum	5.097313e+00
InfectionThroat	.
InfectionViral	-2.451287e+01
Disease_duration	-4.506378e+00
SeverityMild	.
SeverityMild/Moderate	8.920088e+00
SeverityModerate	-1.393311e+01
SeverityModerate/Severe	-6.821032e+01
SeveritySevere	2.667421e+01
Family_ADNo	4.242972e+00
Family_ADYes	-6.696768e-13
Response_endNo	1.190052e+01
Response_endYes	-1.935519e-12
Longest_period	3.559630e+01
SF36_0	-5.815467e+00
SF36_15	6.090438e+00
SF_20_24	.
SF_36	3.022949e+01
Function_0	6.445945e-01
Function_15	-1.483155e+01
Function_24	4.167105e+00
Function_36	-1.555788e+01

Compliance to protocol

Proportion	Uncertainty
p=0.6551724	CI: (0.456638554389758 ,0.814024400938905) SE: 0.0882632273954608

Adverse events

Proportion	Uncertainty
p=0.2758621	CI: (0.134458950851201,0.474851201493499) SE: 0.0829960921123194

Our recommendations for the next trial

Randomized

to eliminate selection bias and ensure that the treatment and control groups are comparable.

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Double-blind

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Placebo-controlled

to accurately attribute effects to the treatment itself.

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- The article provides excessive details about patients' health throughout the study, including minor issues.

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