Usability Study of PF-06410293, an Adalimumab Biosimilar, by Prefilled Pen: Open-Label, Single-Arm, Sub-Study of a Phase 3 Trial in Patients with Rheumatoid Arthritis

Roy M Fleischmann,1 Amy E Bock,2 Wuyan Zhang,3 Charles M Godfrey,4 Ivana Vranic,5 Carol Cronenberger,6 Eva Dokoupilová7

1University of Texas Southwestern Medical Center at Dallas, Metroplex Clinical Research Center, Dallas, TX, USA; 2Pfizer Inc, Cambridge, MA, USA; 3Pfizer Inc, Lake Forest, IL, USA; 4Pfizer R&D UK Ltd, Cambridge, UK; 5Pfizer, Tadworth, UK; 6Pfizer Inc, Collegeville, PA, USA; 7Medical Plus, s.r.o., Uherske Hradiste; Masaryk University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Brno, Czech Republic

Corresponding author: Roy M. Fleischmann; University of Texas, Southwestern Medical Center, Metroplex Clinical Research Center, Dallas, Texas, USA; Email: RFleischmann@arthdocs.com; Phone: +1-214-540-0645; ORCID iD: 0000-0002-6630-1477
**Table.** List of IECs or IRBs for study B5381002 (ClinicalTrials.gov identifier: NCT02480153; EudraCT number: 2014-000352-29)

| Country      | Site Number     | IEC or IRB                                                                 |
|--------------|-----------------|---------------------------------------------------------------------------|
| Australia    | 2252 and 2255   | Bellberry Limited                                                          |
|              | 2253            | Human Research Ethics Committee (TQEH/LMH/MH)                              |
| Brazil       | 2017            | Comitê de Ética em Pesquisa do Hospital de Clinicas da UFPR               |
|              |                 | Comissão Nacional de Ética em Pesquisa                                    |
| Bulgaria     | 2100–2103 and   | Ethics Committee for Multicenter Trials                                   |
|              | 2105            |                                                                           |
| Colombia     | 2025            | Comite de Etica de la Investigacion Riesgo de Fractura S.A.               |
| Czech Republic| 2110, 2111 and  | Eticka komise fakultni nemocnice Brno                                    |
|              | 2115            |                                                                           |
|              | 2113            | Eticka komise Slezske nemocnice v Opave                                  |
|              |                 | Eticka komise fakultni nemocnice Brno                                    |
|              | 2116            | Eticka komise fakultni nemocnice Brno                                    |
|              |                 | Eticka komise Revmatologicky ustav                                      |
| Estonia      | 2118 and 2120   | Tallinn Medical Research Ethics Committee                                  |
| Georgia      | 2126            | EC of V.Tsitlanadze Scientifically-Practical Rheumatology Center LTD      |
|              | 2127            | EC of LTD Cardio-Reanimation Center                                       |
|              | 2128            | EC of LTD.MediClubGeorgia                                                 |
| Country     | Numbers | Committees                                                                 |
|------------|---------|-----------------------------------------------------------------------------|
| Germany    | 2133, 2137, 2140 and 2142–2145 | Ethikkommission der Medizinischen Fakultät der LMU München                  |
| Hungary    | 2147, 2149 and 2150 | Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága    |
| Japan      | 2276    | Anjo Kosei Hospital Institutional Review Board                              |
|            | 2277, 2280 and 2290 | National Hospital Organization Central Review Board                          |
|            | 2278    | Hokkaido University Hospital Institutional Review Board                      |
|            | 2279    | Haradoi Hospital Institutional Review Board                                 |
|            | 2283    | Saitama Medical Center Institutional Review Board                            |
|            | 2284    | Sapporo City General Hospital Institutional Review Board                     |
| Country          | Code       | Review Board                                                                 |
|------------------|------------|-------------------------------------------------------------------------------|
|                 | 2287       | Yokohama Minoru Clinic IRB                                                    |
| Republic of      | 2257       | Seoul National University Hospital Institutional Review Board                  |
| Korea            | 2258       | Chonnam National University Hospital Institutional Review Board               |
| Korea            | 2260       | Severance Hospital, Yonsei University Health System IRB                      |
|                 | 2261       | Hanyang University Seoul Hospital IRB                                         |
|                 | 2262       | Konkuk University Medical Center IRB                                          |
| Lithuania        | 2152–2154  | Lithuanian Bioethics Committee                                                |
| Mexico           | 2033       | Mexico Centre for Clinical Research S.A. de C.V. Comité de Etica en Investigación |
|                 | 2035       | Comité de Etica en Investigacion de Mexico Centre for Clinical Research S.A de C.V |
| New Zealand      | 2265, 2266 and 2269 | Health and Disability Ethics Committee                                      |
| Peru             | 2044, 2049 and 2051 | Comité Institucional de Ética en Investigación de la Asociación Benéfica Prisma |
| Location          | Code  | Ethics Committee                                                                 |
|-------------------|-------|----------------------------------------------------------------------------------|
| Peru              | 2046  | Comité Institucional de Ética en Investigación de la Universidad de San Martín de Porres |
| Poland            | 2155–2170 | Komisja Bioetyczna przy Okręgowej Radzie Lekarskiej                                      |
| Poland            | 2172  | Wielkopolskiej Izby Lekarskiej                                                     |
| Russian Federation| 2173  | EC of GBUZ of Yaroslavl region City hospital n. a.                                  |
| Russian Federation| 2174  | N.A. Semashko Ethics Council under the Ministry of Health of Russian Federation      |
|                  | 2175  | Local Ethics Committee at Orenburg State Medical Academy                            |
|                  | 2176  | Regional Ethics Committee of GBOU VPO KGMU of Ministry of Health of Russian Federation |
|                  | 2177  | EC of GBUZ VO "Regional clinical hospital"                                          |
|                  | 2178  | Ethics Council under the Ministry of Health of Russian Federation                   |
|                  | 2179  | EC of GAUZ of Kemerovo Region "Regional clinical hospital for war veterans"         |
| Ethics Council under the Ministry of Health of Russian Federation | 2180 |
|-----------------------------|------|
| EC of GBUZ Republican hospital n.a. V.A. Baranov | |
| Ethics Council under the Ministry of Health of Russian Federation | 2182 |
| EC of GBUZ of city of Moscow City clinical hospital | |
| EC of GBU of Ryazan region Regional clinical cardiology dispenser | 2183 |
| Ethics Council under the Ministry of Health of Russian Federation | 2184 |
| EC of Spb GBUZ "Clinical rheumatology hospital # 25" | |
| Local Ethics Committee at Municipal Clinical Hospital No. 1 Named after N.I. Pirogov | 2185 |
| EC of LLC Alliance Biomedical Ural group | 2192 |
| Ethics Council under the Ministry of Health of Russian Federation | |
| Serbia | 2186, 2188 and 2189 |
| Local Ethic Committee of the Institute of Rheumatology | |
| Country     | Page/Range | Institutional Body                                                      |
|-------------|------------|------------------------------------------------------------------------|
| South Africa| 2193–2196  | Pharma-Ethics Independent Research Ethics Committee                     |
|             | 2199       |                                                                        |
|             | 2198       | Human Research Ethics Committee of the University of the Witwatersrand |
| Spain       | 2225–2227, 2230 | Comité Ético de Investigación Clínica de la Comunidad Autónoma del País Vasco. CEIC-E. |
| Taiwan      | 2270       | Research Ethics Committee, China Medical University & Hospital         |
|             | 2271       | Institutional Review Board, Chung Shan Medical University Hospital      |
|             | 2273       | Research Ethics Committee A, National Taiwan University Hospital        |
|             | 2274       | TMU-Joint Institutional Review Board                                   |
| Ukraine     | 2201       | Komisiia z pytan etyky Lvivskoho oblasnoho klinichnoho diahnostynchnoho tsentruru |
|             | 2203       | Komisiia z pytan etyky pry komunalnii 4-ii miskii klinichnii likarni m.Lvova |
| United Kingdom          | 2213, 2217, 2219 | Health Research Authority - NRES Committee South and 2220 Central Berkshire |
|------------------------|------------------|--------------------------------------------------------------------------------|
| United States          | 2300, 2301, 2303, 2305, 2308, 2309, 2311–2315, 2319, 2322, 2324, 2327, 2329–2334, 2337, 2340, 2342, 2343, 2347, 2349, 2353 | Schulman Associates IRB                                                                 |
2355, 2356, 2358–
2363, and 2375–
2380

2318 North Mississippi Health Services Institutional Review Board

2354 St Luke's Health System IRB

IEC, Independent Ethics Committee; IRB, Institutional Review Board.
**Fig. S1.** A) PFS and B) PFP devices.

A) PFS device

B) PFP device

*PFP* prefilled pen; *PFS* prefilled syringe
Instructions for Observer Assessment Tool (OAT)

Start the assessment by handing the study materials as outlined in the Subject Study Medication Dosing Booklet and Instructions to the subject or caregiver (user), after they have been trained as outlined in the protocol.

Inform the user that there is no need to hurry. There is no benefit to achieving a shorter time. Doing the procedure CORRECTLY is most important—not speed.

Inform the user that you are there to observe and provide guidance but cannot provide physical assistance during the injection. The only reason for your physical intervention would be to prevent an avoidable injury.

The user should read or refer to the Instructions for Use (IFU)—as much as needed.

If the pre-filled pen (autoinjector) fails to operate, or if the user cannot use the pen so that the injection cannot be performed, document this as a failure in the form (on next page) and provide the user with another pen, but do not provide physical assistance.

Record the injection with the replacement pen on a fresh OAT questionnaire. A pen failure should be dealt with as a device complaint (see Protocol Medical Device Complaint Reporting Requirements).

If the user is able to successfully administer the dose but requires your verbal help to complete the injection, document the specifics below, including asking the user if after the injection they are now confident that they will be able to inject unassisted at home.

If not, provide additional training until you have addressed their confusion or concerns and they confirm their understanding as to how to successfully administer the study drug.

If, following this, in the observer’s judgment the user is not suitable to administer the injection using the pen, the subject should be discontinued from the sub-study and the reasons fully documented.

Based on your observations, did the user successfully inject the full dose into an acceptable injection site without physical assistance?

If this attempt was not successful—why was it not successful? Provide details of the unsuccessful attempt.
(e.g. – pen failed to operate; user removed the pen prematurely from the injection site, resulting in the drug continuing to be expelled from the pen after removal; user was unable to perform a step.)

Where a successful injection was made—did the user need any specific verbal help to achieve it?

Please record the details of all such help provided.
(e.g. – what was the task or step that they could not complete; what additional instruction was required; were they able to complete the injection after the instruction, etc.)

Turn over for questions
**Patient Questionnaire** (only to be completed by the Pen User)

Please complete this questionnaire after each injection. Please make sure that you answer the questions only about the pen you have identified in this first section.

| Subject number | Subject ID |
|----------------|------------|
|                |            |

| What day did you use the pen? | Date |
|-------------------------------|------|
|                                |      |

| What is the pen container label number? (of the pen you used) | Pen container label number |
|---------------------------------------------------------------|---------------------------|
|                                                              |                           |

**Who actually gave the injection?**

- Subject
- A Healthcare Professional
- A relative or friend
- Someone else (please specify)

I had help from: __________________________

It is important that the person who actually gave the injection fills in this questionnaire. Please do not fill this in for someone else if you did not actually give the injection.

**Were the instructions clear enough for you to use without getting any help?**

- Yes
- No—I had help with the instructions from a Healthcare Professional
- No—I had help with the instructions from a relative or friend
- No—I had help with the instructions from elsewhere (please specify)

I had help from: __________________________

Please check which instruction step(s) you had trouble with, below.

- 1 - Things you need
- 2 - Getting ready
- 3 - Check window (before injection)
- 4 - Choose injection area
- 5 - Remove cap
- 6 - Insert needle
- 7 - Inject medicine
- 8 - Withdraw pen
- 9 - Check window (after injection)
- 10 - Dispose
- 11 - After injection

**Which area did you try to inject?**

- Thigh
- Abdomen

**Do you believe that a full dose was injected?**

- Yes
- No

**Were you able to press the button down completely, as shown below?**

- Yes
- No

**Has the blue bar on the pen moved across the window, as shown below?**

- Yes
- No

**Did you have any other problems? (Please check all that apply)**

- No—I did not have any other problems.
- Yes—I could not get the cap off.
  - Please state what happened: __________________________
- Yes—medicine was still flowing out the pen after it was withdrawn from the skin.
- Yes—I did not hear a click at the end of use.
- Yes—I forgot to hold for 5 seconds.
- Other—please give a brief description: __________________________

If you have attempted to use any of the other pens you have been provided, please tell us about them in a fresh questionnaire.

Thank you for your participation.
The purpose of this plain language summary is to help you to understand the findings from recent research.

• Adalimumab and the adalimumab biosimilar PF-06410293 are approved to treat the condition under study that is discussed in this summary.

• The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence not on the results of a single study.

More information can be found in the scientific article of this study, which you can access here: View Scientific Article

What did this study look at?

• This study looked at how successful people were at injecting the adalimumab biosimilar medicine PF-06410293 using a pre-filled pen, which researchers developed to offer patients more convenience.

What is rheumatoid arthritis?

• Rheumatoid arthritis is an autoimmune disease that causes pain, swelling, and stiffness in people’s joints.

  – In people with rheumatoid arthritis, the immune system (the body’s own defense cells) attacks the lining that surrounds their own joints.

  – Over time the cartilage and bones in the joint can become damaged. This can make it hard and/or painful to perform daily activities.

  – Cartilage is a type of connective tissue that is flexible.

  – The hands, feet, and wrists are often affected.

How is rheumatoid arthritis treated?

• People with rheumatoid arthritis often take methotrexate, which works by blocking the immune system to reduce inflammation.

  • If people’s rheumatoid arthritis does not improve with methotrexate, they may also take adalimumab.

  – Adalimumab is a type of biological medicine. It is made from proteins produced naturally by the body.
• Adalimumab works by blocking the activity of a cytokine called tumor necrosis factor alpha (TNFα for short), which is released by immune cells and causes inflammation.
  – Cytokines are proteins that gather immune cells to areas of infection, inflammation, and damage.

• In rheumatoid arthritis, immune cells continue to release TNFα, which causes long-lasting joint inflammation. This can cause painful symptoms.
  – Adalimumab binds to TNFα and stops it from signaling to other immune cells. This reduces inflammation and can reduce painful symptoms.

What are biosimilar medicines?
• Biosimilar medicines are very similar to biological medicines already used by doctors but are less expensive and may increase access to these treatments.
  – Biosimilars are carefully tested to make sure they work as well as biologics and are as safe before they can be used as medicines.

• In a previous study, researchers showed that a biosimilar of adalimumab, known as PF-06410293, was just as safe and effective for treating rheumatoid arthritis.

How do people take adalimumab and PF-06410293?
People take adalimumab and PF-06410293 by injecting it under the skin into their stomach area using a pre-filled syringe, similar to how people with diabetes inject insulin.

Researchers have developed a pre-filled pen to make it easier for people with rheumatoid arthritis to take adalimumab and PF-06410293. Pre-filled pens are single-use and disposable.

In a previous study, researchers showed that adalimumab or PF-06410293 was as safe and effective at treating rheumatoid arthritis in people who changed from a pre-filled syringe to a pre-filled pen.

What was the aim of this study?
• In this study, researchers looked at how successful people were at injecting PF-06410293 using a pre-filled pen.
  – Researchers developed pre-filled pens to offer patients more convenience.

• Researchers measured the successful use of the pre-filled pen by calculating the delivery system success rate.
  – People can check a small window on the pre-filled pen to see if they have used the pre-filled pen successfully.
  – If the blue bar has moved across the window, then they successfully used the pre-filled pen.

Before use or unsuccessful use
Users filled out a questionnaire to report if the injection was successful.

Then, researchers work out the percentage of people who successfully used the pre-filled pen.

Successful use

• Researchers also looked at the side effects that people with rheumatoid arthritis had when taking ADL-PF using the pre-filled pen.
  – A side effect is something (expected or unexpected) that you feel was caused by a medicine or treatment you take.
Where is this study in the drug development timeline?

- This was a sub-study of a larger three-part phase 3 clinical trial that compared the safety and effectiveness of PF-06410293 with adalimumab made in the European Union.
  - A phase 3 clinical trial is a large study (up to thousands of patients) that is long in duration (1–4 years). It looks at how safe a new treatment is and how well it works compared with a standard treatment.
- People could choose to take part in this study if they were already taking part in the larger phase 3 clinical trial.

Who took part in this study and what did they have to do?

**Sub-study (weeks 52–66)**

- After taking part in a 1-year clinical trial, 50 people with rheumatoid arthritis from the United States, Czech Republic, Lithuania, and Poland volunteered for an additional sub-study.
- People with rheumatoid arthritis or their caregivers had training to help them use the pre-filled pen.
  - They injected 40 mg of PF-06410293 once every other week for 6 weeks using the pre-filled pen.
  - They also took 6 mg to 25 mg of methotrexate each week.
- People used the pre-filled pen at home or at the study center where researchers watched them.

Additional information

For more information on this study, please visit:

- View Scientific Article
  - https://clinicaltrials.gov/ct2/show/NCT02480153?term=NCT02480153&draw=2&rank=1
- For more information on clinical studies in general, please visit:
  - https://www.clinicaltrials.gov/ct2/about-studies/learn
• On average, the people in this study were 54 years old.
  – Around 70% were female.
  – About 90% were right-handed.
  – On average, they had been living with rheumatoid arthritis for 8 years.
• No one in the study had previously used a pre-filled pen.
• People could continue using the pre-filled pen after the sub-study ended until the end of the phase 3 clinical trial (week 78) if they chose to.
• Researchers monitored people’s rheumatoid arthritis during the study.

What were the results of the study?

How successful were people at using the prefilled-pen to inject PF-06410293?

Everyone used the pen successfully to inject all 6 doses

96 in 100 reports were by people with rheumatoid arthritis who self-injected PF-06410293

4 in 100 reports were by caregivers for someone with rheumatoid arthritis

1 person received 5 injections from a non-professional caregiver and 1 injection from a professional caregiver

This means that the delivery system success rate score was 100%

What were the side effects of treatment?

• Researchers looked at how many people had side effects after treatment.
  – A side effect is considered “serious” when it is life-threatening, needs hospital care, or causes lasting problems.
  – The side effects could be for any reason and may not be due to taking the study drug.
  – Researchers looked at side effects in everyone who took at least part of one dose of PF-06410293 using a pre-filled pen.
Adalimumab  
Biosimilar  
Cytokine  
Methotrexate  
Rheumatoid arthritis  
Tumor necrosis factor alpha

No one died during this sub-study  
No one had a reaction at the site of injection  
No one left the study or stopped treatment because of side effects

10 in 100 people had an upper respiratory tract infection

All other side effects were reported by 4 in 100 people or fewer

3 people reported 3 serious side effects:  
1 person had tonsillitis  
1 person had rheumatoid arthritis that worsened  
1 person fractured their pelvis

Side effects of this sub study were similar to those reported in the overall clinical trial

How many people continued using the pre-filled pen to inject PF-06410293 when the sub-study finished?

96 in 100 people chose to continue using the pre-filled pen for the rest of the trial

4 in 100 people chose to switch back to using the pre-filled syringe for the rest of the trial

More results from this study can be found here: View Scientific Article

Additional information

For more information on this study, please visit: View Scientific Article

https://clinicaltrials.gov/ct2/show/NCT02480153?term=NCT02480153&draw=2&rank=1

For more information on clinical studies in general, please visit: https://www.clinicaltrials.gov/ct2/about-studies/learn
What were the main conclusions reported by the researchers?

- These findings suggest that people with rheumatoid arthritis and their caregivers can safely and effectively inject PF-06410293 using a pre-filled pen.
- Side effects in people with rheumatoid arthritis using a pre-filled pen to inject PF-06410293 were similar to those in people with rheumatoid arthritis using a pre-filled syringe.
- Most people chose to continue injecting PF-06410293 using a pre-filled pen instead of a pre-filled syringe for the rest of the clinical trial.
- Researchers could not be certain
  - how well people injecting PF-06410293 using a pre-filled pen would have responded without previous experience using a pre-filled syringe.
  - that people with rheumatoid arthritis would receive similar training on how to use the pre-filled pen in a real-world setting.

Are there any plans for further studies?

- There are currently no plans for further studies of PF-06410293 using a pre-filled pen.

Who sponsored this study?

Pfizer Inc.
235 East 42nd Street, NY, NY 10017
Phone (United States): +1 212-733-2323
Pfizer would like to thank all of the people who took part in this study.

Acknowledgements
Writing support was provided by Jake Evans, PhD, and Elyse Smith, PhD, Engage Scientific Solutions, and was funded by Pfizer.

Additional information
For more information on this study, please visit:
https://clinicaltrials.gov/ct2/show/NCT02480153?term=NCT02480153&draw=2&rank=1

For more information on clinical studies in general, please visit:
https://www.clinicaltrials.gov/ct2/about-studies/learn