

Supplementary Appendix

Impact of headache and over-the-counter treatment on pain and functional and cognitive parameters: A real-world study across three geographies

Running title:

Effectiveness of proven treatments on headache relief and association with functional and cognitive recovery

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Supplementary Appendix

Participant eDiary

Item from Study Outline

Enrolment

1. How old are you? [Enter a number]
1. _____ (years)
2. What is your gender?
 1. Male
 2. Female
 3. Intersex
 4. Prefer not to answer
5. What is your primary employment status?
 6. Employed full-time
 1. Employed part-time (39 or less hours per week)
 2. Not currently employed
 3. Student
 4. Retired
 5. I prefer not to answer
6. Have you been diagnosed with any of the following chronic diseases?
 1. Diabetes
 2. Hypertension
 3. Stroke
4. How long ago have you been experiencing headaches?
 1. 6 months to one year ago
 2. More than 1 year but less than 2 years ago
 3. More than 2 years ago
4. What type of headache do you usually experience?
 5. Headache
 6. Migraine

Programming Notes

Numerical input. Allow integer values from 18 and up

Dropdown list

Single response allowed

Dropdown list

Single response allowed

Yes/no for each disease

Question 6: Yes/No for each type

7. Unknown
- 6a. Did a healthcare provider diagnose your headache?
8. Yes
9. No
- 6a.1 What type of healthcare provider diagnosed your headache?
10. General practitioner
11. Specialist (e.g., neurologist or pain specialist)
12. Other
13. How often do you usually experience headache episodes? [Select a number]
14. Less than once a week
15. Once a week
16. Twice a week
17. Three times per week
18. More than three times per week
19. Do you usually use (*Sanofi local brand*) for your headache (in other words, do you keep (*Sanofi local brand*) at home to use when you have a headache)?
20. Yes
21. No
22. Why do you use (*Sanofi local brand*)? (select all that apply)
23. Doctor prescription (general practitioner, specialist)
24. Pharmacist's recommendation
25. Relative's recommendation
26. Self-decision
27. Publicity
28. Other
- If unknown is selected, no other responses allowed; if headache type selected, unknown not allowed.
- If headache type selected, ask question 6a.
- If Yes to question 6a., ask question 6a.1
- If No to question 6a., skip to question 7.
- Dropdown list
- Single response allowed
- Yes/No
- If no, exit after question 9
- Yes/no for each reason

Study observational period (is defined as the period from Day 1 to the first headache episode, within a maximum period of 15 days)

Thank you for your continued participation in this headache study.

This reminder is sent to the participants each morning.

1. Please remember to complete the diary as soon as you feel a headache today. If the participant does not report at least one headache within 15 days, he/she is withdrawn from the study.

Study Evaluation period (is defined as a period of 15 days from the first headache episode to the end of the participant's involvement). These questions are completed for each headache episode experienced during the 15-day evaluation period.

Thank you for your continued participation in this headache study.

This reminder is sent to the participants each morning.

2. Please remember to complete the diary as soon as you feel a headache today.

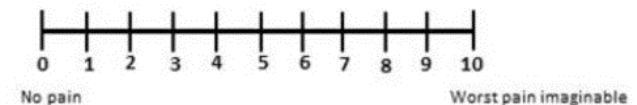
Before taking any medication or starting any therapeutic approach

1. What type of headache are you experiencing?
2. Headache
3. Migraine
4. Unknown
5. On a scale of 0 to 10, how painful is your headache now?
NRS 0 (no pain) to 10 (worst pain imaginable)

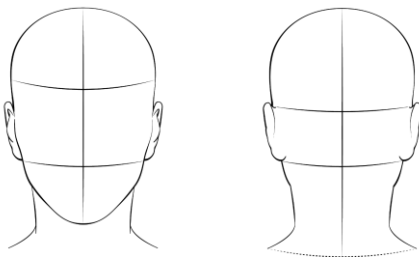
Dropdown list

Single response allowed

NRS scale



6. Please indicate on the picture where you feel the pain.



Participant will be able to tap on region(s) where pain is located.

Head regions will be divided as 6 equal regions in the front and 6 equal regions in the back of the head

Multiple responses allowed

- | | | |
|-----|--|--------------------------|
| 7. | Are you having any of the following headache-related symptoms? | Yes/no for each question |
| 8. | Nausea | |
| 9. | Vomiting | |
| 10. | Pain worsening if moving | |
| 11. | Sensitivity to light (photophobia) | |
| 12. | Sensitivity to noise | |
| 13. | How much is your headache impacting your ability to concentrate now?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 14. | How much is your headache impacting your ability to be attentive now?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 15. | How much is your headache impacting your ability to focus now?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 16. | How much is your headache impacting your ability to coordinate multiple activities now?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 17. | How much is your headache impacting your ability to be productive at doing things now?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 18. | How much is your headache impacting your ability to think clearly now?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 19. | How much is your headache impacting your energy now?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |

Thank you for answering the questions. You may now take medication for your headache, if you decide so. You will receive a notice in 2 hours. Please click the link in this notice when you receive it to answer some more questions about your headache.

Two hours later, a notification is sent to participants to complete the next questions (Q.12 to 23)

Please complete the next questions now.

20. Did you take any medication for your headache episode?

1. Yes

2. No

If yes:

1. Which medication did you take?

1. (Sanofi local brand)

2. Other headache medication

2. How long ago did you take the medication?

1. Less than 1.5 hours

2. Between 1.5 and 2.5 hours

3. More than 2.5 hours

3. Did you use any of the following approaches for your headache episode?

1. Sleep

2. Ice on my head

3. Darkness

4. Drink caffeine

5. Other

4. On a scale of 0 to 10, how painful is your headache now?

NRS 0 (no pain) to 10 (worst pain imaginable)

5. How much is your headache impacting your ability to concentrate now?

NRS 0 (no impact) to 10 (severe impact)

6. How much is your headache impacting your ability to be attentive now?

NRS 0 (no impact) to 10 (severe impact)

7. How much is your headache impacting your ability to focus now?

NRS 0 (no impact) to 10 (severe impact)

yes/no

If yes, ask 12a. and 12b.

If no, go to question 13

12a. Drop down list; Multiple responses are allowed

12b. Multiple responses are allowed

This question appears to each selection made in 12b.

Yes/no for each therapy

NRS scale

NRS scale

NRS scale

NRS scale

- | | | |
|-----|--|--|
| 8. | How much is your headache impacting your ability to coordinate multiple activities <u>now</u> ?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 9. | How much is your headache impacting your ability to be productive at doing things <u>now</u> ?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 10. | How much is your headache impacting your ability to think clearly <u>now</u> ?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 11. | How much is your headache impacting your energy <u>now</u> ?
NRS 0 (no impact) to 10 (severe impact) | NRS scale |
| 12. | How did your headache affect your work/school? | Yes/No for each activity |
| 13. | I missed work/school, or I could not do these activities today | Single response only |
| 14. | I was slower at work/school | This question is specific to participants who work or go to school), refer to question 3 |
| 15. | How did your headache affect the following daily activities? | Yes/No for each activity |
| 16. | I was slower at home duties | |
| 17. | I missed social activities, or I could not take part in social activities today | |
| 18. | I missed family time | |
| 19. | I could not use a device with a screen (e.g., phone, computer, television) | |
| 20. | I could not function | |

NRS, numeric rating scale.

Supplementary Table 1. Reasons for exclusion from the enrolled, eligible, and full analysis sets in each country.

	Germany (n = 9572)	Brazil (n = 1315)	Japan (n = 21,736)
Excluded from enrolled set	9,146	954	21,284
Duplicate attempt	274 (3%)	168 (18%)	214 (1%)
Did not complete screener	1,172 (13%)	290 (30%)	2,025 (10%)
No informed consent	295 (3%)	167 (18%)	902 (4%)
Inclusion criteria not met	3,079 (34%)	190 (20%)	11,646 (55%)
Exclusion criteria met	4,326 (47%)	139 (15%)	6,497 (31%)
Excluded from eligible set	133	100	126
Did not download app	92 (69%)	58 (58%)	98 (78%)
No headache episode within 15 days after enrolment	27 (20%)	8 (8%)	14 (11%)
No 2-hour baseline pain NRS	14 (11%)	34 (34%)	14 (11%)
Excluded from full analysis set	91	52	130
No headache episode treated with OTC treatment only with baseline and 2-hour post-treatment pain NRS assessment within 1.5 hours and 2.5 hours	89 (98%)	52 (100%)	130 (100%)
Withdrew	2 (2%)	0	0

NRS, numeric rating scale; OTC, over-the-counter.

Supplementary Table 2. Kendall's Tau coefficients for association between pain intensity and cognitive and functional parameters for the German ($n = 293$), Brazilian ($n = 261$), and Japanese ($n = 326$) cohorts (eligibility set).

Germany	Pain intensity			
	Baseline		Two hours post-treatment	
	Kendall's Tau coefficient	<i>P</i> -value	Kendall's Tau coefficient	<i>P</i> -value
Ability to concentrate	0.4730	<0.0001	0.2557	0.0034
Ability to be attentive	0.3765	<0.0001	0.2356	0.0048
Ability to focus	0.3253	<0.0001	0.2702	0.0017
Ability to think clearly	0.3099	0.0001	0.2275	0.0065
Ability to coordinate multiple activities	0.2904	0.0003	0.2715	0.0012
Ability to be productive at doing things	0.2473	0.0021	0.2101	0.0091
Energy	0.2385	0.0027	0.1980	0.0128

Brazil	Pain intensity			
	Baseline		Two hours post-treatment	
	Kendall's Tau coefficient	<i>P</i> -value	Kendall's Tau coefficient	<i>P</i> -value
Ability to concentrate	0.3585	<0.0001	0.1648	0.0387
Ability to be attentive	0.3451	<0.0001	0.1516	0.0531
Ability to focus	0.3146	<0.0001	0.1600	0.0388

Ability to think clearly	0.2553	0.0009	0.0858	0.2703
Ability to coordinate multiple activities	0.3111	<0.0001	0.0962	0.2063
Ability to be productive at doing things	0.2582	0.0008	0.1189	0.1225
Energy	0.2447	0.0014	0.1481	0.0504

Japan	Pain intensity			
	Baseline		Two hours post-treatment	
	Kendall's Tau coefficient	<i>P</i>-value	Kendall's Tau coefficient	<i>P</i>-value
Ability to concentrate	0.4128	<0.0001	0.3467	0.0002
Ability to be attentive	0.3724	<0.0001	0.3287	0.0003
Ability to focus	0.4043	<0.0001	0.3323	0.0003
Ability to think clearly	0.3571	<0.0001	0.3021	0.0005
Ability to coordinate multiple activities	0.4026	<0.0001	0.3272	0.0003
Ability to be productive at doing things	0.3194	<0.0001	0.3256	0.0002
Energy	0.2977	0.0003	0.2966	0.0005

Supplementary Table 3. Impact of headache on work/school and daily activities according to pain severity in the overall study population (full analysis set)

	Headache severity (<i>n</i> = 1,718 episodes reported by 607 participants)			
	Mild	Moderate	Severe	All
Pain impact on work/school, <i>n</i> (%)				
I missed work/school, or I could not do these activities today	3 (0.2%)	78 (4.5%)	121 (7.0%)	202 (11.8%)
I was slower at work/school	28 (1.6%)	221 (12.9%)	338 (19.7%)	587 (34.2%)
Pain impact on daily activities, <i>n</i> (%)				
I was slower at home duties	81 (4.7%)	379 (22.1%)	594 (34.6%)	1,054 (61.4%)
I missed social activities, or I could not take part in social activities today	29 (1.7%)	192 (11.2%)	296 (17.2%)	517 (30.1%)
I missed family time	21 (1.2%)	147 (8.6%)	242 (14.1%)	410 (23.9%)
I could not use a device with a screen (e.g., phone, computer, television)	42 (2.4%)	232 (13.5%)	404 (23.5%)	678 (39.5%)
I could not function	12 (0.7%)	179 (10.4%)	334 (19.4%)	525 (30.6%)

Supplementary Table 4. Responder/non-responder sensitivity analysis: Descriptive association between categorized pain intensity numeric rating scale (NRS) score and cognitive and functional recovery in the full analysis set*

Germany (n = 202)			Brazil (n = 209)			Japan (n = 196)		
	Pain intensity assessed via NRS score during the first headache episode after 2 hours of OTC treatment							
	Responder¹ (n = 171) 84.7%	Non-responder² (n = 31) 15.3%		Responder¹ (n = 174) 83.3%	Non-responder² (n = 35) 16.7%		Responder¹ (n = 165) 84.2%	Non-responder² (n = 31) 15.8%
Concentration recovery** (n = 180)	163 (95.3%)	17 (54.8%)	Concentration recovery** (n = 180)	165 (94.8%)	15 (42.9%)	Concentration recovery** (n = 170)	155 (93.9%)	15 (48.4%)
Attention recovery** (n = 180)	164 (95.9%)	16 (51.6%)	Attention recovery** (n = 176)	161 (92.5%)	15 (42.9%)	Attention recovery** (n = 168)	156 (94.5%)	12 (38.7%)
Focus recovery** (n = 180)	164 (95.9%)	16 (51.6%)	Focus recovery** (n = 173)	159 (91.4%)	14 (40.0%)	Focus recovery** (n = 167)	153 (92.7%)	14 (45.2%)
Thinking clearly recovery** (n = 172)	160 (93.6%)	12 (38.7%)	Thinking clearly recovery** (n = 176)	160 (92.0%)	16 (45.7%)	Thinking clearly recovery** (n = 176)	156 (94.5%)	20 (64.5%)

Coordination recovery** (n = 183)	164 (95.9%)	19 (61.3%)	Coordination recovery** (n = 176)	160 (92.0%)	16 (45.7%)	Coordination recovery** (n = 168)	153 (92.7%)	15 (48.4%)
Productivity recovery** (n = 179)	164 (95.9%)	15 (48.4%)	Productivity recovery** (n = 175)	159 (91.4%)	16 (45.7%)	Productivity recovery** (n = 173)	155 (93.9%)	18 (58.1%)
Energy recovery** (n = 176)	162 (94.7%)	14 (45.2%)	Energy recovery** (n = 178)	161 (92.5%)	17 (48.6%)	Energy recovery** (n = 172)	155 (93.9%)	17 (54.8%)

¹Responder: decrease in $\geq 30\%$ NRS pain intensity from baseline; ²Non-responder: participants who did not meet the definition for responder

**Recovery is defined as $\geq 20\%$ improvement in NRS score from baseline to 2 hours post-treatment

NRS, numeric rating scale; OTC, over-the-counter.