This supplement contains the following items:

1. Original protocol, final protocol, (summary of changes: no changes have been made in the protocol).

2. Original statistical analysis plan, final statistical analysis plan, (summary of changes: no changes have been made in the statistical analysis).

Clopidogrel On Top of Aspirin For the Prevention of New Onset Migraine Headache Occurrence Following Transcatheter Closure of Atrial Septal Defects: A Prospective Randomized Trial (the CANOA study)

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TABLE OF CONTENTS

BACKGROUND

Many studies have demonstrated a significant reduction in or even an abolition of migraine headaches following transcatheter closure of atrial septal defects (ASD) or patent foramen ovale (PFO) (1). On the other hand, it has been reported that new-onset migraine headaches can also occur following atrial septal device implantation in adult and pediatric patients with no previous history of migraine (2-5). Monterlmans et al (6) reported a 17% incidence of new-onset migraine headaches within two months following transcatheter ASD closure in 75 patients. New-onset migraine headaches occurred more frequently with larger ASD devices and persisted for at least 6 months in all cases. Yew et al (7) found an incidence of 8% of new-onset migraine headaches following transcatheter ASD closure in a series of 25 consecutive patients. We carried out a study including a series of 260 consecutive patients who underwent transcatheter ASD or PFO closure (8). All patients underwent an interview using a structured headache questionnaire that focused on 3 periods: before ASD-PFO closure, within the 3 months following ASD-PFO closure and at 23 ± 17 months follow-up. The presence and characteristics of headaches were recorded for each of these 3 periods, and all questionnaires were evaluated by a neurologist who determined whether or not headaches were migraines, with or without aura, according to the International Headache Society criteria (9). Migraine headache was considered to be associated with transcatheter ASD-PFO closure if it occurred within the 30 days following the procedure in patients with no previous episodes of migraine headache at any time before the procedure. The results of the study showed a 7% incidence of new-onset migraine headaches following the procedure. The first migraine headache episode occurred within the 2 weeks following the procedure in most patients and migraine was associated with aura in 69% of the cases. Patients who had new-onset migraine headaches were younger, tended to be more frequently females, and all of them underwent ASD closure instead of PFO closure. Multivariate analysis showed that transcatheter ASD closure was the only independent predictor of new-onset

migraine headache occurrence (incidence of migraine headaches of 12% following ASD closure compared to 0% after PFO closure). While the number and severity of migraine headaches decreased over time, about two thirds of the patients continued to suffer migraine headaches after a mean follow-up of 2 years.

The choice and duration of antithrombotic treatment following ASD closure has evolved empirically, with aspirin for at least 6 months being the therapy most frequently used (10). In fact, most of the patients with migraine headaches following ASD closure that have been reported up to now were on aspirin therapy. In our previous study regarding the incidence of migraine headaches after ASD closure 83% of patients were treated with aspirin, 14% received clopidogrel alone or a combination of aspirin + clopidogrel, and 3% were on warfarin therapy. Interestingly, none of the patients receiving clopidogrel had migraine headaches following the procedure, compared with 12% of the patients treated with aspirin alone. Preliminary retrospective and observational studies have suggested that the addition of clopidogrel on top of aspirin was associated with a 72% to 100% reduction of migraine attacks following transcatheter ASD closure (11,12). Based on these preliminary reports, some centers have started using aspirin + clopidogrel (75 mg/die between 6 weeks and 3 months after ASD closure) as the antithrombotic treatment following transcatheter ASD closure, but no prospective randomized studies have yet confirmed such data.

HYPOTHESIS

The addition of clopidogrel on top of aspirin may reduce the occurrence of new-onset migraine headache episodes following transcatheter ASD closure.

OBJECTIVE

To evaluate the incidence and severity of new-onset migraine headache episodes following transcatheter ASD closure in patients treated with aspirin alone compared to those on aspirin + clopidogrel therapy as antithrombotic treatment after the procedure.

PRIMARY END-POINT

Mean number of monthly migraine days per patient within the 3 months following transcatheter ASD closure.

SECONDARY END-POINTS

1. Severity of migraine attacks following ASD closure as evaluated by the intensity of migraine episodes and the Migraine Disability Assessment (MIDAS) questionnaire at 3-month follow-up after ASD closure.
2. Incidence of bleeding complications at 3-month follow-up.
3. Percentage of patients with new-onset migraine attacks.
4. Time to first migraine episode.
5. Percentage of patients with migraine headaches at 6-month and 1-year follow-up (exploratory only according to local feasibility).

INCLUSION CRITERIA

1. Patients ≥ 18 year old undergoing transcatheter ASD closure with the Amplatzer Septal Occluder device (AGA medical Corp., MN, USA).
2. Female subjects must be post-menopausal, surgically sterile, or using an effective method of birth control.
3. Signed an informed consent document.

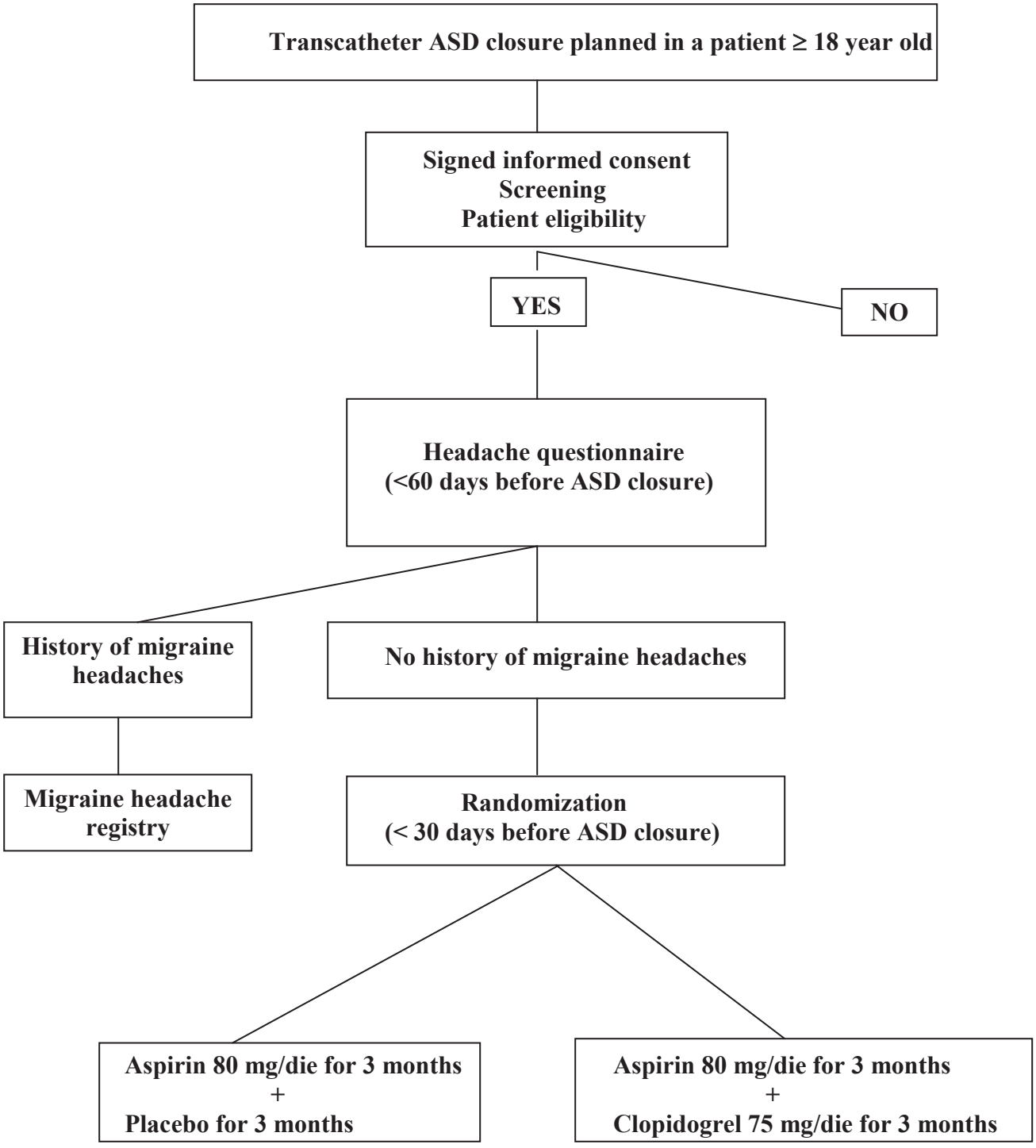
EXCLUSION CRITERIA

1. Allergy or intolerance to any of the antithrombotic drugs (aspirin, clopidogrel) used in the study.
2. Need for anticoagulation therapy.
3. Use of ASD closure devices other than the Amplatzer Septal Occluder device.
4. History of migraine headaches (based on migraine headache questionnaire).
5. Refusal to sign the informed consent.
6. Pregnancy or breast-feeding or planning to become pregnant during the study.
7. Previous stroke.

STUDY DESIGN

This is a prospective, randomized, double blind, multicenter study, including patients with no previous history of migraine attacks who have been diagnosed with an ASD and for whom transcatheter ASD closure has been clinically indicated. Patients will be randomized either to aspirin (80 mg/day) or aspirin (80 mg/day) + clopidogrel (75 mg/day) for 3 months following ASD closure. The occurrence and severity of migraine headaches will be evaluated by a neurologist using a

structured headache questionnaire at 1 month and 3 months following ASD closure. An additional 6 month and 1 year follow-up evaluation will be exploratory according to local feasibility.



	<60 days before ASD closure	<30 days before ASD closure	1 month after ASD closure	3 months after ASD closure[1]
Screening	**X**			
Randomization		**X**		
Migraine Headache questionnaire assessment	**X**		**X**	**X**

1: An additional 6 months and 1 year follow-up will be exploratory according to local feasibility, to evaluate percentage of patients with migraine headaches following ASD closure.

SAMPLE SIZE

Based on previous studies (6-8), the expected percentage of patients who will suffer new-onset migraine attacks following ASD closure will be 15%, and these patients will have a median number of 5 migraines per month (interquartile range 1 to 23 days) within the 3 months following the procedure. The addition of clopidogrel therapy is expected to reduce the incidence and number of migraine headaches by at least 50% (11,12). The appropriate sample size calculation, considering that many patients will have no migraine headaches, is Poisson regression (13) which can be executed using SAS Proc Genmod. The Poisson regression model will include treatment group as a class effect and a covariate capturing the baseline monthly migraine rate. In addition, a repeated statement for patient should be included in SAS Proc Genmod statements to control for over dispersion and not to inflate the underlying variation, i.e. providing robust standard errors based on empirical-type estimates. Therefore, we will model the mean number of migraine days per month by patient (including those who won't have migraine attacks) by a mixture of:

- zero-truncated Poisson distribution and,
- zero-constant distribution

The power of the test has been computed for several samples sizes by Monte Carlo simulations, and a total number of 70 patients per group would be necessary to have 80% power to detect differences

between groups with a *P* value <0.05. Considering the possibility of 5% to 10% dropouts during the follow-up period, the sample size will be increased to a total of 150 patients.

STUDY PROCEDURES AND ASSESSMENTS

I. Transcatheter ASD closure

All procedures will be performed by femoral approach, with transesophageal or intracardiac echocardiography guidance. Heparine (100 U/Kg) will be administered in all cases. The Amplatzer ASD device will be used in all cases.

II. Antithrombotic treatment

1. **Aspirin**

Aspirin (80 mg/die) will be administered in all cases. The first dose of aspirin will be administered at least 1 day before ASD closure and continued for 3 months after ASD closure. After this period, the duration of aspirin treatment will be left at the criteria of the investigator.

2. **Clopidogrel vs. placebo**

Patients will be randomized to antithrombotic treatment with clopidogrel (75 mg/die) vs. placebo. The first dose of clopidogrel or placebo will be administered 1 day before the procedure and continued for 3 months.

III. Evaluation of migraine headaches

The occurrence, characteristics and severity of headaches will be evaluated by an interview using a structured headache questionnaire (see Appendix I). Also, patients will have a headache diary where the occurrence, characteristics and severity of headaches will be noted (see Appendix II). The questionnaires will be evaluated by a neurologist blinded to group assignment who will determine

whether or not headaches are migraines, with or without aura, according to the International Headache Society criteria (9). Headache severity will be evaluated by the number (per month), duration (hours), and intensity (from 1 = minimal to 10 = very severe) of headache attacks. Headache-related disability burden will be evaluated by the Migraine Disability Assessment (MIDAS) questionnaire and a MIDAS score was obtained for all patients for each of the 3 time periods. The MIDAS score is calculated as the sum of missed days and days when productivity was reduced by at least half for work outside home and for house work, as well as missed days of non-work activities (family, social, and leisure) during a 3-month period.

The interview including the headache questionnaire will be held at the following times:

- Within the 15 days before ASD closure
- Thirty days after ASD closure (± 5 days)
- Ninety days after ASD closure (± 7 days)
- One-hundred and eighty days after ASD closure (± 14 days) (exploratory only)
- Three-hundred and sixty days after ASD closure (± 14 days) (exploratory only)

Headache questionnaires will be sent to the Quebec Heart Institute – Laval Hospital and all of them will be evaluated by a neurologist who will establish whether the headaches are migraines and if they are associated or not with aura. In doubtful cases, the neurologist will be allowed to make an interview (phone call or clinical visit) to better determine the characteristics of patient headaches and finally establish the diagnosis of migraine or non-migraine headache, with or without aura.

PREMATURE WITHDRAWAL / DISCONTINUATION CRITERIA

A premature withdrawal is defined as a study discontinuation which occurs after the patient has taken at least 1 dose of study medication. Patients who discontinue from the study medication will be withdrawn from the study.

Every effort should be made to conduct a follow-up for patients who withdraw or are withdrawn from the study prematurely.

STATISTICAL ANALYSIS

Qualitative variables will be expressed as percentages and quantitative variables as mean (standard deviation) or median (interquartile range). Comparison of numerical variables will be performed using the Student´s t test or Wilcoxon rank sum test depending on variable distribution. Comparaison of the mean number of monthly migraine days will be performed using the Poisson regression model. Differences will be considered statistically significant at *P* values <0.05. The data will be analyzed using SAS statistical software version 9.1.3 (SAS Institute Inc., Cary, NC).

ADVERSE EVENT REPORTING

SUSARs will be collected as per sanofi-aventis Pharma Inc. requirements

DEFINITIONS

«Adverse Event»: any untoward medical occurrence in a subject or clinical investigation subject during the period of observation in the clinical study and which does not necessarily have to have a causal relationship with this treatment.

«Serious adverse event (SAE) or serious adverse reaction»: any untoward medical occurrence that at any dose: results in death, or is life-threatening, or requires in-patient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, or is considered as an important medical event.

«Related SAE»: there is a reasonable possibility according to the investigator and/or the sponsor that the product may have caused the event.

«SUSAR»: «Suspected Unexpected Serious Adverse Reaction»: a serious adverse drug reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or Canadian Product Monograph for an authorised product).

Researcher shall

a. file a Clinical Trial Application with Health Canada and provide sanofi-aventis with a copy of the Non Objection Letter (NOL) from Health Canada;

b. conduct the Study according to the Protocol that the Researcher has provided to sanofi-aventis;

c. conduct the Study in accordance with all applicable laws and government regulations including but not limited to the Canada Food and Drugs Act and all regulations made pursuant thereto, Health Canada's Therapeutic Products Directorate Guidelines, ICH Harmonized Tripartite Good Clinical Practice Consolidated Guideline ("ICH/GCP Guideline"), and the Tri-Council Policy Statement, "Ethical Conduct for Research Involving Humans", as stipulated in the referenced Protocol;

d. be responsible for all safety reporting to Health Canada in accordance with ICH Guidelines, the Food & Drugs Act and as specified in the Guidance for Clinical Trial Sponsors. Such responsibilities include but are not limited to expedited reporting of SUSARs to Health Canada. The reference document for evaluating expectedness shall be the Canadian product monograph.

e. forward a copy of all SUSARs (initial and any follow-up) submitted to Health Canada in the context of the Study, at time of submission, to:

sanofi-aventis Canada Inc. ("sanofi-aventis") Pharmacovigilance
by fax at (514) 333-2956
attention: Diana Basmadjian, Pharmacovigilance Head

f. All such reports shall be in English. In addition to such reports, any other relevant safety reports submitted to Health Canada shall be forwarded to sanofi-aventis Pharmacovigilance at time of submission. The Researcher agrees to assist with all reasonable requests by sanofi-aventis Pharmacovigilance to ensure that all safety reports are sufficiently investigated, including, but not limited to, requests to seek additional information relating to the safety reports.

g. keep sanofi-aventis Pharmacovigilance informed of any significant safety issues, events or results, e.g. Data Safety Monitoring Board recommendations, occurring or found during the course of the Study, which might affect performance thereof, within twenty-four (24) hours or on the next working day of receiving such communication. The Researcher shall notify sanofi-aventis Pharmacovigilance of any communication received from any governmental entity relating to any safety issue for the Study Drug within twenty-four (24) hours or on the next working day of receiving such communication. Sanofi-aventis Global Pharmacovigilance and Epidemiology shall be involved as needed.

h. be responsible for information to participating investigators and ethics committees including, but not limited to the distribution of SUSARs.

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APPENDIX I

QUESTIONNAIRE SUR LA MIGRAINE

Souffrez-vous de maux de tête ? ☐ Oui ☐ Non

Si oui, remplir les parties A, B, C et D (Ne pas compléter la partie D à 30 jours)

Y a-t-il des antécédents de migraines dans votre famille (père, mère)? ☐ Oui ☐ Non

PARTIE A

Au cours d'une crise quel type de mal de tête avez-vous ?

- L'intensité du mal de tête est : 0 1 2 3 4 5 6 7 8 9 10
  (de 0 a 10, 0 = léger, 10 = très sévère) (encercler la réponse)
- D'un seul coté de la tête ☐ Oui ☐ Non
- Pulsatile ou battante ☐ Oui ☐ Non
- Aggravé par l'activité physique normale ☐ Oui ☐ Non

PARTIE B

Quels autres symptômes avez-vous pendant les crises ?

- Maux de cœur (nausée ou vomissement) ☐ Oui ☐ Non
- Tendance à éviter la lumière, ☐ Oui ☐ Non
- Tendance à éviter les bruits ☐ Oui ☐ Non
- Troubles visuels (zig-zag lumineux, points scintillants) ☐ Oui ☐ Non
- Picotements, engourdissement du visage ou des mains ☐ Oui ☐ Non
- Larmes involontaires, nez bouché, yeux rouges ☐ Oui ☐ Non
- Difficulté à parler avant ou pendant le mal de tête ☐ Oui ☐ Non
- Perte de force au niveau des bras ou des jambes ☐ Oui ☐ Non

PARTIE C

Pour ce qui est de vos maux de tête…

- Ils ont une durée (moyenne) de _____minutes

- Combien de jours avez-vous mal à la tête en moyenne par mois ? ____ /mois

- La fréquence de vos maux de tête est de :
Veuillez cocher la réponse la plus appropriée à votre situation

☐ moins d'un par mois (nombre de fois par année, en moyenne ____)
☐ un par mois
☐ plusieurs fois par mois (nombre de fois, en moyenne ____)
☐ un par semaine
☐ plusieurs fois par semaine (nombre de fois, en moyenne ____)
☐ un par jour
☐ plusieurs fois par jour (nombre de fois, en moyenne ____)

- Lors de vos maux de tête devez-vous réduire votre travail ?
Veuillez cocher la réponse la plus appropriée à votre situation

☐ Toujours (100%)
☐ Souvent (75%)
☐ Parfois (50%)
☐ Rarement (10%)
☐ Jamais (0%)

- Lors de vos maux de tête devez-vous réduire vos activités familiales ou sociales (repas, sorties ou rendez-vous) ?:
Veuillez cocher la réponse la plus appropriée à votre situation

☐ Toujours (100%)
☐ Souvent (75%)
☐ Parfois (50%)
☐ Rarement (10%)
☐ Jamais (0%)

PARTIE D

Limitations reliées aux vos maux de tête dans les derniers 3 mois.

- Combien de jours de travail ou d'école avez-vous perdu dans les derniers 3 mois à cause de vos maux tête ? _____ jours

- Combien de jours dans les derniers 3 mois votre productivité au travail ou à l'école a diminué de la moitié ou plus à cause de vos maux de tête ? *(n'incluez pas les jours que vous avez indiqués dans la question précédente où vous avez manqué des journées de travail ou école)* _____ jours

- Combien de jours dans les dernier 3 mois vous n'avez pas effectué de travaux domestiques à cause de vos maux de tête ? _____ jours

- Combien de jours dans les derniers 3 mois votre productivité dans les travaux domestiques a diminué de la moitié ou plus à cause de vos maux de tête ? *(n'incluez pas les jours que vous avez indiqués dans la question précédente où vous n'avez pas fait de travaux domestique)* _____ jours

- Combien de jours dans les derniers 3 mois vous n'avez pas fait d'activités en famille, sociales ou de loisir à cause de vos maux de tête ? _____ jours

- Combien de jours de mal de tête avez-vous eu dans les derniers 3 mois ? _____ jours

- Dans une échele de 0 a 10, comment évaluez-vous l'intensité de vos maux de tête ? *(0 : pas de douleur, 10 : le pire douleur possible)* 0 1 2 3 4 5 6 7 8 9 10 (encercler la réponse)

MIGRAINE QUESTIONNAIRE

Do you have headaches? ☐ Yes ☐ No

If you answered yes, please fill sections A, B, C and D (Don't fulfill section D at 30 days)

Is there any history of migraine headaches in your family (father, mother)? ☐ Yes ☐ No

SECTION A

What kind of headache do you experience?

- Headache intensity is: (0 to 10, 0 = no pain, 10 = very severe) 0 1 2 3 4 5 6 7 8 9 10 (surround the answer)
- Only one side of the head? ☐ Yes ☐ No
- Throbbing pain? ☐ Yes ☐ No
- Worsened by usual physical activity? ☐ Yes ☐ No

SECTION B

Do you experience other symptoms during headache episodes

- Nausea or vomiting ☐ Yes ☐ No
- Tendency to avoid light ☐ Yes ☐ No
- Tendency to avoid sounds ☐ Yes ☐ No
- Visual disturbances (zigzag lights, scintillating points) ☐ Yes ☐ No
- Tingling or numbness on the face or limbs ☐ Yes ☐ No
- Involuntary tears, nasal stuffiness, red eyes ☐ Yes ☐ No
- Language difficulties before or during headache ☐ Yes ☐ No
- Loss of strength in arms or legs ☐ Yes ☐ No

SECTION C

Concerning your headache…

- The (average) headache duration is _____minutes

- How many days per month (on average) do you have headaches? ____ /month

- The frequency of your headaches is:
Please check the answer corresponding to your situation

☐ Less than once a month (Average number per year ____)
☐ Once a month
☐ Several times per month (Average number ____)
☐ Once a week
☐ Several times per week (Average number ____)
☐ Once a day__
☐ Several times a day (Average number ____)

- Do headaches limit your regular work?
Please check the answer corresponding to your situation

☐ Always (100%)
☐ Often (75%)
☐ Sometimes (50%)
☐ Seldom (10%)
☐ Never (0%)

- Do headaches limit your social or family life? (i.e.: meals, leisure or appointments)
Please check the answer corresponding to your situation

☐ Always (100%)
☐ Often (75%)
☐ Sometimes (50%)
☐ Seldom (10%)
☐ Never (0%)

SECTION D

Limitations linked to your headaches in the last 3 months.

- How many days in the last 3 months you missed work or school because of your headaches? _____ days

- How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches?
(Do not include days you counted in question 1 where you missed work or school) _____ days

- How many days in the last 3 months you did not do household work because of your headaches? _____ days

- How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches?
(Do not include days you counted in question 3 where you did not do household work) _____ days

- How many days in the last 3 months did you miss family, social or leisure activities because of your headaches? _____ days

- How many days in the last 3 months did you have a headache?
(If a headache lasted more than 1 day, count each day) _____ days

- On a scale of 0-10, on average how painful were these headaches? 0 1 2 3 4 5 6 7 8 9 10 (to surround the answer)
(Where 0 = no pain at all, and 10 = pain as bad as it can be)

APPENDIX II JOURNAL DES MAUX DE TÊTE

MOIS _____ ANNÉE _____

Jour	Maux de tête (oui – non)	Intensité (1 à 10) *	Durée		Symptômes	Médicaments et posologie
			Début (heure)	Fin (heure)		
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						

*** Échelle d'intensité du mal de tête : 1= léger 10= très sévère**

HEADACHE DIARY

MONTH _____ YEAR _____

Day	Headache (yes– no)	Intensity (1 to 10) *	Duration		Symptoms	Medication and dose
			Start (hour)	End (hour)		
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						

*** Headache intensity scale: 1= mild 10= very severe**