# CLINICAL STUDY PROTOCOL

## 〔PROTOCOL TITLE〕

The role of migraine prophylaxis agent topiramate in treating patients with sudden sensorineural hearing loss

VERSION NO.6

DATES (20220812)

INVESTIGATORS

SITES

NCT05403229

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**Section** **Page**

# 1. Synopsis

**Protocol Title：**

The role of migraine prophylaxis agent in treating patients with sudden sensorineural hearing loss – A randomized controlled trial

**Study Objectives：**

To understand the efficacy of migraine prophylaxis agent "topiramate" in treating patients with sudden sensorineural hearing loss

**Investigational product(s)：**

Topiramate

**Development Phase**：☐ I ☐II ☐III ☐IV ☐others_____ V not applicable

**Study Design：**

1. v Experimental Group
   v Control Group ： ☐ Placebo
   ☐ Study Drug (Name、Dose、Usage) _____
   v Other __standard systemic steroid with/without intratympanic steroid_
2. Blinding：v Open ☐ Evaluator-blind ☐ Single-blind(patient) ☐ Double-blind(patient+PI)
   ☐ Double Dummy ☐ Other _____
3. Randomization: v Yes ☐ No
4. ☐ Parallel design ☐ Crossover design ☐ Other _____ v Not applicable
5. Treatment Period：_____6 weeks_____ ☐ Not applicable
6. Study Period: _____1____year (or From DD/MM/YYYY to DD/MM/YYYY)
6. Dose adjustment：v Mandatory ☐ Selectively ☐ No ☐ Not applicable
7. Study location：☐ Single v Multi-center ☐ Global

**Endpoints (Outcome measure)：**

1. Primary endpoint:
   The improvement rate and gain of pure tone audiometry **(compare day 0 and day 84)**
2. Secondary endpoints:
   The improvement rate and gain of **word recognition score (compare day 0 and day 84)**
   The improvement rate and gain of pure tone audiometry **(compare day 0 and day 56)**
3. Exploratory endpoints (if any): nil

**Inclusion/Exclusion Criteria：**

Inclusion criteria
1. Age > 20
2. Confirmed diagnosis of unilateral sudden sensorineural hearing loss(SSNHL)
3. Treatment started 14 days within onset of SSNHL

Exclusion criteria
1. Previous SSNHL history

2. Previous middle ear disorder such as chronic otitis media, or previous ear surgery
3. Meniere's disease and fluctuating hearing loss patients
4. Pregnancy or trying to become pregnant
5. Leukemia, hemodialysis, and patients who received chemotherapy before.
6. Previous head and neck radiotherapy
7. Cerebellopontine (CP) angle tumor such as vestibular schwannoma
8. Patients with moderate to severe hepatic insufficiency
9. Patients with major depression disorder or suicide attempt
10. Patients with glaucoma

**Study Procedures：**

1. Expected inclusion patient number (enrolled number: **140**; evaluable number: **112**)
   The participants would be divided into two group, half in the experimental group and the other half in the control group.
2. All patients will receive audiometry examination, laboratory examination, magnetic resonance imaging of brain or auditory brainstem response at the first visit. Then the patient would be followed at the clinic weekly till the sixth week. Audiometry examination will be arranged during the first week and then monthly till 12 weeks.
3. As for the treatment, the control group will receive systemic steroid with/without intratympanic steroid for 2 weeks as the standard therapy for sudden sensorineural hearing loss. The experimental group will receive systemic steroid with/without intratympanic steroid for 2 weeks and simultaneously oral topiramate for 6 weeks.
4. There will be no specimen collection in this study.
5. The patients' gender, age, initial and final hearing threshold, laboratory examination result, audiometry result and symptoms will be collected.

**Concomitant Treatments：** ☐not applicable

**1.** Concomitant Therapy：Prescribe systemic steroid with/without intratympanic steroid

**2.** Prohibited Therapy：nil

**Statistical Methods：**

**1.** Main study Hypothesis：**V** Equality ☐ Superiority ☐ Non-inferiority ☐ Equivalence ☐ Other _____

**2.** Estimated Sample Size：Anticipated enrolled size___140____，Estimated evaluable number __112____

Anticipated enrolled size in our center___**45**____，Estimated evaluable number in our center___**40**___

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**Two-Sample T-Tests Assuming Equal Variance**

**Numeric Results for Two-Sample T-Test Assuming Equal Variance**
Alternative Hypothesis: H1: δ = μ1 - μ2 ≠ 0

| Target Power | Actual Power | N1 | N2 | N | μ1 | μ2 | δ | σ | Alpha |
|---|---|---|---|---|---|---|---|---|---|
| 0.80 | 0.80630 | 56 | 56 | 112 | 12.0 | 19.0 | -7.0 | 13.0 | 0.050 |

**References**
Julious, S. A. 2010. Sample Sizes for Clinical Trials. Chapman & Hall/CRC. Boca Raton, FL.
Chow, S. C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research (Second Edition). Chapman & Hall/CRC. Boca Raton, FL.
Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, MA.
Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.

**Report Definitions**
Target Power is the desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.
Actual Power is the power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.
N1 and N2 are the number of items sampled from each population.
N is the total sample size, N1 + N2.
μ1 and μ2 are the assumed population means.
δ = μ1 - μ2 is the difference between population means at which power and sample size calculations are made.
σ is the assumed population standard deviation for each of the two groups.
Alpha is the probability of rejecting a true null hypothesis.

**Summary Statements**
Group sample sizes of 56 and 56 achieve 80.630% power to reject the null hypothesis of equal means when the population mean difference is μ1 - μ2 = 12.0 - 19.0 = -7.0 with a standard deviation for both groups of 13.0 and with a significance level (alpha) of 0.050 using a two-sided two-sample equal-variance t-test.

*Missing rate =10%, thus the enrollment size is 112/0.9=125

*Missing rate =20%, thus the enrollment size is 112/0.8=140

**3.** Efficacy assessment group： V Intent-to-treat (ITT) ☐ Per-Protocol (**PP**)
☐ Other _____

**4.** Interim analysis： ☐ Yes V No

**5.** Statistical methods : t test will be performed to compare pre- and posttreatment audiometric measurements. Chi-square and independent sample t test will be used to compare categorical and numerical variables between the two groups, respectively.

**6.** Handling of Missing Data : The cases with missing data will be omitted. The remaining data will be analyzed to determine the efficacy of study drug.

# 2. Introduction and Rationale

## 2.1 Investigational product(s)

Topiramate is an anticonvulsant agent with multiple mechanism. The ability of preventing migraine attack was demonstrated by previous randomized controlled trials. It is an oral tablet with well tolerability. When using this agent to prevent migraine, the dosage started from 25mg per day and could be titrated up to 100mg per day.

## 2.2 Animal and preclinical study data

Not applicable

## 2.3 Clinical data

Migraine and sudden sensorineural hearing loss(SSNHL) are two related disorder. Systemic steroid is usually used to treat SSNHL but the role of migraine prophylaxis medication remained unknown. Mehdi Abouzari et al. found a better improvement when combining topiramate and nortriptyline with steroid in a retrospective study. However, a prospective study with randomization is needed to elucidate the efficacy of these agents.

## 2.4 Risks / benefits Assessment

Topiramate is a safe medication that has been already used in treatment of migraine prophylaxis and seizure. The potential adverse effects of topiramate includes mild disturbance in taste, loss of appetite, paresthesia of distal extremities, and increase fetal oral cleft risk. Therefore, children, adolescents and pregnant women were excluded from this study.

The possible benefit from using topiramate in this study is the possible better audiometry improvement.

## 2.5 Regulatory

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

# 3. Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| Primary | |
| 1.To understand the treatment effects of Topiramate for sudden sensorineural hearing loss | 1.Pure tone audiometry improvement (day 0 and day 84) |
| Secondary | |
| 1.To understand the **additional treatment effects** of topiramate for sudden hearing loss events | 1. **word recognition score improvement (compare day 0 and day 84)**<br>2. The improvement rate and gain of pure tone audiometry **(compare day 0 and day 56)** |

# 4. Study Design

## 4.1 Overall Design

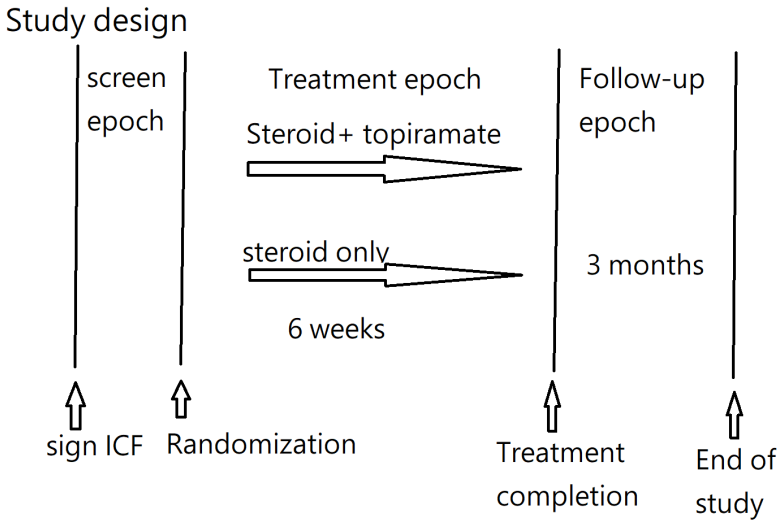
This is a clinical study using medication approved and currently prescribed in the clinic. The included patients were those who came to clinic and was diagnosed as SSNHL within 14 days of

onset. Those patients were asked whether they agreed to participate this clinical trial. Patients who were diagnosed as SSNHL but was later found to be other disease such as Meniere's disease, CP angle tumor will be excluded from this study.

The involved patients were randomized divided into two groups. **(The randomization was based on computer-generated random numbers.)**
Both groups received systemic steroid with/without intratympanic steroid. The experimental group receive additional oral topiramate for 6 weeks.
Follow-up time is 3 months.

This study is multi-center.
Location of the study is performed at Chang gung memorial hospital Linkou branch, Taipei branch, Taoyuan branch, and New Taipei Municipal Tucheng Hospital.

## Flow Chart：



## 4.2 Number of Patients

Enrolled number : **140**
Failed during screening : **10**
Drop-out number : **28**
Estimated evaluable number : **112** ( experimental group 56, control group 56 )

## 4.3 Schedule of Activities

### Time-Event scheme(評估時程表):

| Phase | Screening | Treatment | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|
| Day | 0 | 0 | 7 | 14 | 21 | 28 | 56 | 84 |
| Clinic visit | X | X | X | X | X | X | X | X |
| Screening/administration/safety | | | | | | | | |
| ICF/assent form | X | | | | | | | |
| Inclusion/Exclusion criteria | X | | | | | | | |
| Medical and surgical history | X | | | | | | | |
| Lab exam | X | | | | | | | |
| MRI or ABR exam | X | | | | | | | |
| Randomization/Administration | | | | | | | | |
| Randomization | X | | | | | | | |
| Administration of study drug | X | X | X | X | X | X | | |
| Efficacy/Safety | | | | | | | | |
| Symptoms | | | X | X | X | X | X | |
| Audiometry | X | | | | | | X | X |

**The physician confirm that the patient meets the inclusion criteria at the initial visit (day 0). Then the patients would be asked if he/she is willing to participate into this clinical trial. If the patient agreed, then medical history taking, audiometry and lab examination, MRI or ABR examination will be arranged at same time. He/she will be randomized into either experimental arm or control arm. The treatment will be started immediately. The blood test will be performed at first visit and the data will be checked at day 7. Patients in both arms would follow up at our clinic at day 7,14,21,28,56, and 84. Pure tone audiometry and speech audiometry will be followed at day 56 and 84. Symptoms and adverse effects (safety monitoring) will be followed up at day 7,14,21,28, and 56.**

# 5. Study Population

## 5.1 Inclusion Criteria

Inclusion criteria:
（1）Age > 20

(2) Confirmed diagnosis of unilateral sudden sensorineural hearing loss(SSNHL)
(3) Treatment started 14 days within onset of SSNHL

The diagnostic criteria of SSNHL:
A subset of sudden hearing loss that (a) is sensorineural in nature, (b) occurs within a 72-hour window, and (c) consists of a decrease in hearing of >= 30 decibels affecting at least 3 consecutive frequencies.

The diagnostic criteria of vestibular migraine:
A. At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 hours
B. Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD)
C. One or more migraine features with at least 50% of the vestibular episodes:
- headache with at least two of the following characteristics:

one sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity
- photophobia and phonophobia,
- visual aura

D. Not better accounted for by another vestibular or ICHD diagnosis

## 5.2 Exclusion Criteria

Exclusion criteria:
(1) Previous SSNHL history
(2) Previous middle ear disorder such as chronic otitis media, or previous ear surgery
(3) Meniere's disease and fluctuating hearing loss patients
(4) Pregnancy or trying to become pregnant
(5) Leukemia, hemodialysis, and patients who received chemotherapy before.
(6) Previous head and neck radiotherapy
(7) CP angle tumor such as vestibular schwannoma
(8) Patients with moderate to severe hepatic insufficiency
(9) Patients with major depression disorder or suicide attempt
(10) Patients with glaucoma

## 5.3 Withdrawal criteria

Withdraw from the study:
Participants of this study can withdraw from this study at any time when the patient disagree the consent, or had intolerable adverse effects after medication, or could not follow the treatment protocol.
The data of the withdraw patients will be excluded from the audiometry analysis. The reason of withdrawal would be analyzed and reported.

# 6. Treatments

## 6.1.Treatment Administration

Both experimental group and control group will receive systemic steroid with/without intratympanic steroid as the standard treatment for sudden sensorineural hearing loss. The total duration of systemic steroid is 2 weeks.

As for the experimental group, topiramate 25 mg orally before bedtime with weekly escalation of 25 mg up to 100 mg. **More specifically, the patient will receive 25mg daily at first week. Then the dose will be titrated up to 50mg in the second week, 75mg in the third week, and 100mg daily during the 4-6 weeks.**

The dose of topiramate will be half in patients with renal insufficiency ($Cl_{CR} \leq 70$ mL/min).

## 6.2. Concomitant Therapy

Both experimental group and control group will receive systemic steroid with/without intratympanic steroid as the standard treatment for sudden sensorineural hearing loss.

Hyperbaric oxygen therapy, a common therapy for sudden sensorineural hearing loss, is also allowed in these patients.

# 7. Efficacy Assessments

The evaluation of hearing ability is performed by pure tone audiometry, speech audiometry and **word recognition test(WRS)**.

The audiometry will be arranged during the first clinic visit and followed **at day 56 and day 84**. Then the differences of the pre- and posttreatment audiometry will be evaluated.

**The pure-tone average(PTA) calculated using 0.5-, 1-, 2-, and 3-kHz air conduction thresholds. The WRS is presented as percentage. The treatment efficacy compares the difference of PTA and WRS before and after treatment.**

# 8. Safety Assessments

The most frequent side effects of the study drug are mild disturbance in taste, appetite, and paresthesia of distal extremities. There are no major adverse events reported in previous clinical trials. Those symptoms will be monitored and recorded during each clinical follow-up (from the first clinic to the end of follow-up after 3 months).

# 9. Adverse event reporting

Bang-Yan, Zhang will report SAEs to the IRB of Chang Gung Medical Foundation according to the Serious Adverse Event Reporting Procedures and Guidelines as posted in the Clinical Trials Resource on the website of Chang Gung Medical Foundation IRB. SAE reports to the IRB should include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- Protocol number

- Title of protocol
- Description of the SAE, including attribution to drug and expectedness

## 9.1 Definitions and reports of Adverse Events

All adverse events that occur after the informed consent is signed (including run-in) must be recorded on the adverse event CRF (paper and/or electronic) whether or not related to study agent. AE Data Elements including:

- AE reported date
- AE Verbatim Term
- CTCAE Term (v 5.0)
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a Serious Adverse Event (SAE)
- Action taken with the study agent
- Outcome of the event
- Comments

Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed.

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as follows:

| Grade | Severity | Description |
|---|---|---|
| 1 | Mild | • Barely noticeable, does not influence functioning<br>• Causing no limitations of usual activities |
| 2 | Moderate | • Makes participant uncomfortable, influences functioning<br>• Causing some limitations of usual activities |
| 3 | Severe | • Severe discomfort, treatment needed<br>• Severe and undesirable, causing inability to carry out usual activities |
| 4 | Life threatening | • Immediate risk of death<br>• Life threatening or disabling |
| 5 | Fatal | • Causes death of the participant |

The possibility that the adverse event is related to study drug will be classified as one of the following: not related, unlikely, possible, probable, definite.

**DEFINITION of Serious Adverse Events**: ICH Guideline E2A and GCP of Taiwan define serious adverse events as those events, occurring at any dose, which meet any of the following criteria:

- Results in death

- Is life threatening (Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.

## 9.2 Adverse event follow-up

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such. Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the IRB of Chang Gung Medical Foundation of SAE form in the appropriate format. Follow-up information should be sent to Chang Gung Medical Foundation IRB as soon as possible according to IRB's Serious Adverse Event Reporting Procedures and Guidelines.

# 10. Criteria for the termination of the trial

The trial can be ended before the planned end date because of evidence of adverse effects (harm), or likelihood of failing to reject the null hypothesis (futility)

# 11. Statistical Considerations

t test will be performed to compare pre- and posttreatment audiometric measurements. Chi-square and independent sample t test will be used to compare categorical and numerical variables between the two groups, respectively.

## 11.1 Sample size Determination

The study will be powered to approximately 80% assuming a standard deviation of 13 at an alpha of 0.05. The number of patients required to observe a 5dB difference between the experimental group and control group is about **56** patients in each group if the superiority margin at 0.05. The total estimated patients number required is **112**. Consider the patient with incomplete data and drop-out rate of 20%, the total estimated number of sample size is about **140**.

## 11.2 Planned Statistical methods of analysis

**Statistical analysis**

Quantitative variables will be presented as mean± standard deviation (SD) and categorical variables will be presented as proportions. Paired samples t test will be performed to compare pre- and posttreatment audiometric measurements. Chi-square and independent sample t test

will be used to compare categorical and numerical variables between the two groups, respectively.
The data will be evaluated at the end of study. The expected study period is 1 year.
There will be an interim analysis.

### 11.2.1 Efficacy analysis

The audiometry data will be evaluated at the end of study. Pure tone average (PTA) was measured in accordance with the Committee on Hearing and Equilibrium Guidelines, utilizing thresholds at frequencies of 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. The hearing recovery is defined as a more than 10 dB hearing gain.

### 11.2.2 Safety analysis

The medication used in this study is well studied in the previous clinical trials. The possible adverse effects of the medication will be monitored during each follow-up. The adverse effects of the medication will be analyzed at the end of study.

### 11.2.3 Additional analysis

Nil

### 11.2.4 The level of significance

A p-value less than 0.05 was considered significant and was denoted by *.

### 11.3 Analysis Population

All eligible participants will be included in the analyses. If the participant wishes to withdraw due to any reason after enrollment, the data will also be reported.

### 11.4 Procedure for accounting for missing, unused and spurious data

The incomplete clinical data and sequencing data with poor quality will be excluded in the study.

### 11.5 Procedures for reporting any deviation(s) from the original statistical plan

Any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate.

## 12. Direct access to source data/documents

Investigators permit IRB to access to the source data of experiment for trial-related monitoring, audits, and regulatory inspection.

## 13. Ethical considerations

This study will be conducted according to Taiwan and international standards of Good Clinical Practice for all studies. Applicable government regulations and Chang Gung Medical Foundation research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the Chang Gung Medical Foundation Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

# 14. Data handling and keeping

Clinical data will be collected in Chang Gung Medical Foundation. The sequencing data will be stored in computers of laboratory with an electronic encryption. The clinical and source data can only be assessed by clinical doctors and investigators of the study. The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

# 15. Financing and Insurance

There is no conflict of interest in this study. The research funding sources is from CMRP. The medication used in this study is prescribed commonly in the clinic and no additional insurance is applied for the participants.

# 16. References

The mechanism of migraine and sudden hearing loss is not fully understood. Neurovascular damage or dysfunction are proposed etiology but could be the result of disease. Currently, many clinical trials have been done and the main focus is to prevent migraine attack. But the effects on hearing recovery after sudden hearing loss remained unknown. Mehdi Abouzari et al. reported a better low tone hearing recovery when combining adjuvant migraine medications with conventional steroid therapy. This retrospective study utilized topiramate and nortriptyline in the experimental group. However, the true treatment efficacy of these agents remained unknown. Therefore, a prospective study using single migraine prophylaxis agent in this condition may better elucidate the effects of hearing recovery.

Reference :

Abouzari M, Goshtasbi K, Chua JT, Tan D, Sarna B, Saber T, Lin HW, Djalilian HR. Adjuvant Migraine Medications in the Treatment of Sudden Sensorineural Hearing Loss. Laryngoscope. 2021 Jan;131(1):E283-E288. doi: 10.1002/lary.28618. Epub 2020 Apr 3. PMID: 32243585; PMCID: PMC8011356.