

**1. Titre du résumé :** Challenges and Limitations of Neuromodulation in Addiction Treatment: Results of a Phase II, Non-Comparative, Fleming-Type, Randomized, Double-Blind, Sham-Controlled Trial in Tobacco Use Disorder

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**4. Description précise des objectifs**

Recent neuromodulation data from trials in addiction settings suggest therapeutic promise for neuromodulation interventions. However, important areas of uncertainty remain. We report the results of Tabacstim3, a Fleming-type, phase II, randomized, double-blind, sham-controlled study. This trial was conducted to assess whether active high-frequency repetitive transcranial magnetic stimulation (HF-rTMS), used in combination with nicotine replacement therapy (NRT), is suitable for evaluation in a phase III smoking cessation trial.

**5. Matériel et méthodes**

Participants underwent 16 HF-rTMS sessions: 10 sessions delivered over five consecutive days, followed by 6 maintenance sessions over the subsequent 5 weeks. The primary outcome was the biochemically confirmed continuous abstinence rate (CAR) at 6 weeks post-randomization in the active rTMS group. Secondary outcomes included craving assessments using a visual analog scale. Randomization and double-blinding were implemented to minimize assessment bias and to evaluate the feasibility of maintaining masking, thereby strengthening the study's internal validity and informing the design of a subsequent phase III trial.

**6. Résultats et conclusions**

Seventy-eight participants were randomized to the active (n = 39) and sham (n = 39) groups. Participants in the active group had fewer psychiatric comorbidities, but higher craving scores at baseline. At the 6-week follow-up, 18 participants in the active rTMS group were abstinent (46.2%). According to our predefined criterion for treatment efficacy, active HF-rTMS may therefore be considered effective and suitable for evaluation in a phase III trial. However, this finding should be interpreted with caution, as the sham rTMS group showed similar outcomes, with 23 participants (59.0%) abstinent at 6 weeks. Craving scores decreased to a greater extent in the active HF-rTMS group ( $-2.53 \pm 3.11$  vs.  $-1.61 \pm 3.14$ ).

During the presentation, the results will be discussed in relation to the challenges and limitations of neuromodulation trials in substance use disorders, as well as future perspectives for optimizing neuromodulation treatments.

## **7. Liens d'intérêt :**

Nous certifions que notre travail ne présente aucun lien avec l'industrie pharmaceutique, du tabac, de l'alcool, de la cigarette électronique et avec les compagnies de jeux.

Déclaration des liens d'intérêt :

AD BRISTOL MYERS SQUIBB (hospitalité), ETHYPHARM (Contrat de participation à une manifestation, hospitalité), CAMURUS (parrainage)

KG pas de lien d'intérêt

BT CAMURUS (Contrat de conseil, contrat de recherche, hospitalité, parrainage), ETHYPHARM (Contrat de participation à une manifestation, contrat d'expert scientifique, hospitalité), BOUCHARA – RECORDATI (hospitalité), SMART PHARMA CONSULTING (Enquête, étude, étude de marché), ELIVIE (Contrat de participation à une manifestation)

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