

Tetrahydrocannabinol (THC) / Cannabidiol (CBD) Oral Solution in Combination with Temozolomide (TMZ) and Radiotherapy (RT) in Patients with Newly Diagnosed Glioblastoma: Phase Ib GEINO-1601 Trial

Juan Manuel Sepúlveda¹, Mírlam Alonso², Gabriel Velilla³, Clara García Grove², María Martínez-García⁴, Palmira Foro⁵, Cristina García Gonzalez⁶, Carolina Muriel Lopez⁶, Raquel Luque⁷, Natalia Luque⁸, Agostina Stradella⁹, Paula Sabat⁹, Miguel Navarro Martín¹⁰, Beatriz Rivas López¹⁰, Manuel Guzmán¹¹, Elena Tovar-Ambel¹², Guillermo Velasco¹², Raúl Sánchez Morillas¹³, José Fuster Salva¹³

¹Medical Oncology Service, Neuro-Oncology Unit, Hospital Universitario 12 de Octubre, Madrid, Spain. ²Medical Oncology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain. ³Neurology Service, Neuro-Oncology Unit, Hospital Universitario 12 de Octubre, Madrid, Spain. ⁴Medical Oncology Department, Hospital del Mar, Barcelona, Spain. ⁵Radiation Oncology Department, Hospital del Mar, Barcelona, Spain. ⁶UGC Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen de la Victoria, IBIMA, Málaga, Spain. ⁷Medical Oncology Department, Hospital Universitario Virgen de las Nieves, Instituto de Investigación Biomédica de Granada, Granada, Spain. ⁸Medical Oncology Department, Hospital Universitario de Jaén, Jaén, Spain. ⁹Medical Oncology Department, Institut Català d'Oncologia (ICO) L'Hospitalet, L'Hospitalet de Llobregat, Barcelona, Spain. ¹⁰Medical Oncology Department, Hospital Universitario de Salamanca, Salamanca, Spain. ¹¹Biochemistry and Molecular Biology Department, Complutense University of Madrid, CIBERNED & IRYCIS, Madrid, Spain. ¹²Biochemistry and Molecular Biology Department, Complutense University of Madrid & IDISSC, Madrid, Spain. ¹³Medical Oncology Department, Hospital Universitario Son Espases, Palma de Mallorca, Spain.

BACKGROUND

- Glioblastoma (GBM) is the most common, and most aggressive, malignant primary brain tumour of adults.^{1,2} Resistance to frontline temozolomide (TMZ) is a common treatment complication for patients with glioblastoma (GBM).³
- THC / CBD enhance autophagy and apoptosis when combined with TMZ in preclinical models of GBM and may overcome TMZ resistance in glioblastoma (GBM).⁴⁻⁶
- Here we present the safety results after ending the inclusion of all expected patients in the GEINO1601 clinical trial with a median follow-up of 10.3 weeks (95% CI: 8-15). The efficacy results will be presented with longer

OBJECTIVES

- To assess the safety of Tilray PS Oral Solution T10:C10 (THC+CBD) combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma.
- The primary objective is to determine the maximum tolerated dose of THC/CBD according to NC CTCAE V5.0.

METHODS

- GEINO-1601 is an open-label, single arm, phase Ib trial run in Spain including patients with newly diagnosed GBM according to WHO2021 classification, aged ≥18 years and ≤70 years to evaluate the association of cannabinoids with RT/TMZ. Patients with psychiatric, psychotic or cognitive disorders, cardiovascular diseases and those previously exposed to cannabis were excluded. The study planned to enroll 30 patients.
- THC/CBD 10 mg/ml each as oral solution is administered continuously in combination with RT/TMZ and 6 cycles of TMZ (Stupp scheme) followed by maintenance with THC/CBD monotherapy.
- Patients receive 5 mg/day during week 1 and intra-pts doses are escalated weekly up to 80 mg/day. Self-titrated dose escalation is stopped in case of toxicity or bad tolerance in case of grade 3-4 hematologic toxicities or accumulative low grade toxicities (figure 1).

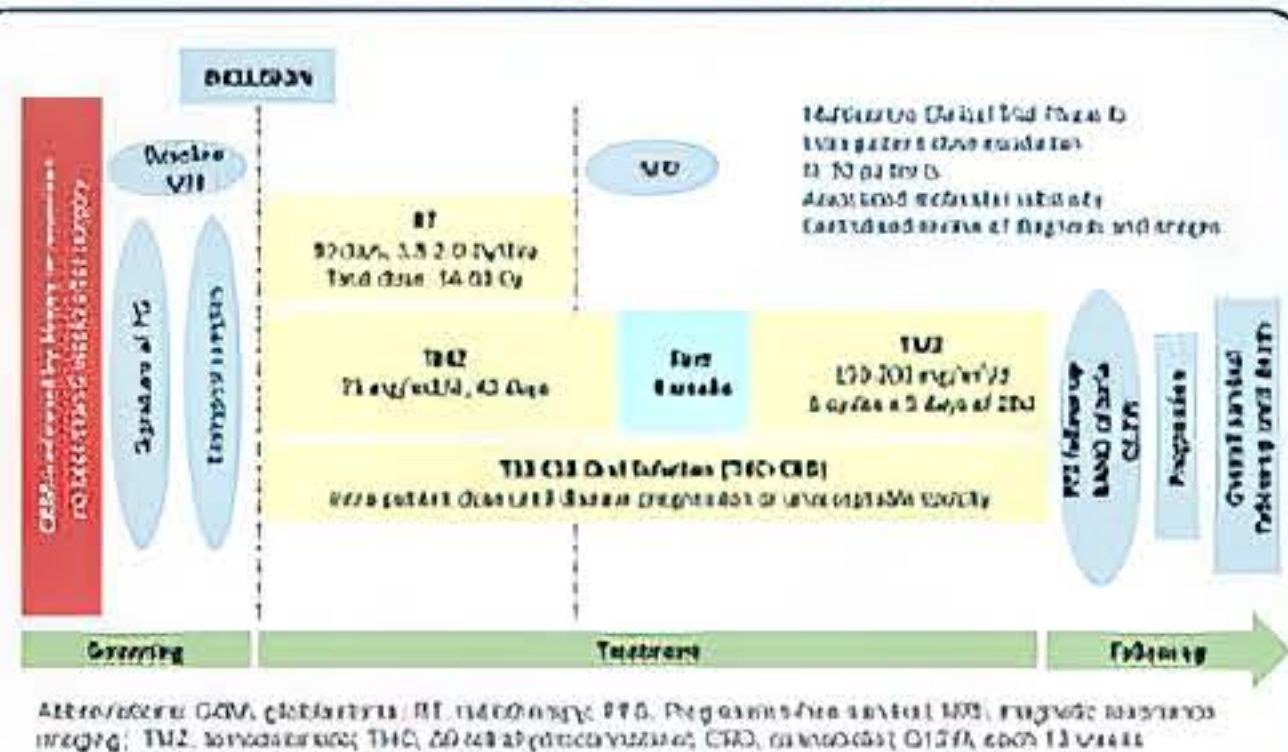


Figure 1. Study design



Figure 2. Flow Patients

REFERENCES

- Stupp R, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005
- Mugala M, et al. Advances and challenges in the treatment of glioblastoma: A clinician's perspective. *Discovery Medicine* 2013
- Patrick Y, et al. Malignant Gliomas in Adults. *N Engl J Med* 2008
- Torres S, et al. A combined preclinical therapy of cannabinoids and temozolomide against glioma. *Mol. Cancer Ther.* (2011).
- Twelves R, et al. A phase Ib randomised, placebo-controlled trial of nabiximols cannabinoid oromucosal spray with temozolomide in patients with recurrent glioblastoma. *Br J Cancer*. 2021
- Doherty R. Cannabinoids in glioblastoma: multi-forme-type or hope? *Br J Cancer*. 2021

RESULTS

- From Sep 2023 to Apr 2024, 32 patients were included, and 29 received THC/CBD, fulfilling the expected sample size (figure 2).
- The median age (N=32) was 61 years (range: 28-71) and 50% were female. Patients characteristics are described in the table 1.
- The self-titrated dose escalation is underway and the maximum dose was already reached in 22 patients after a median time for reaching maximum dose of 7.4 weeks (95% CI: 4-8.1). The maximum pre-specified dose of 80 mg/day was reached by 10 (34.5%) patients (figure 3, 4 and 6).
- One patient discontinued treatment by toxicity and 72.4 % of patients continue on treatment (figure 5).
- Serious adverse events (AEs) related to study treatments were reported in 1 patients (3.4%), who experienced G4 neutropenia and thrombocytopenia related to TMZ.
- Grade 3-4 AEs were hematologic events (13.8%) related to TMZ (figure 7). No Grade 3-4 AEs related to THC/CBD were reported. Grade 1-2 AEs related to THC/CBD occurred in 25 pts, most frequent asthenia (37.9%), nausea (37.9%), somnolence (34.5%), vomiting (17.2%) and dizziness (13.8%), showing no clear dose dependency (figure 8).

Table 1. Baseline Characteristics

Characteristic	N = 29
Median age; (range)	61.5 (57.5-65.3)
Sex, n (%)	
Male	13 (44.8)
Female	16 (55.2)
Karnofsky index (KPS); n (%)	
90-100	16 (55.2)
70-80	13 (44.8)
60-70	0
<60	0
Surgical procedure, n (%)	
Complete resection	14 (48.3)
Biopsy	7 (24.1)
Subtotal resection (75%-90%)	4 (13.8)
Partial resection (25%-75%)	3 (10.3)
UK	1 (3.4)

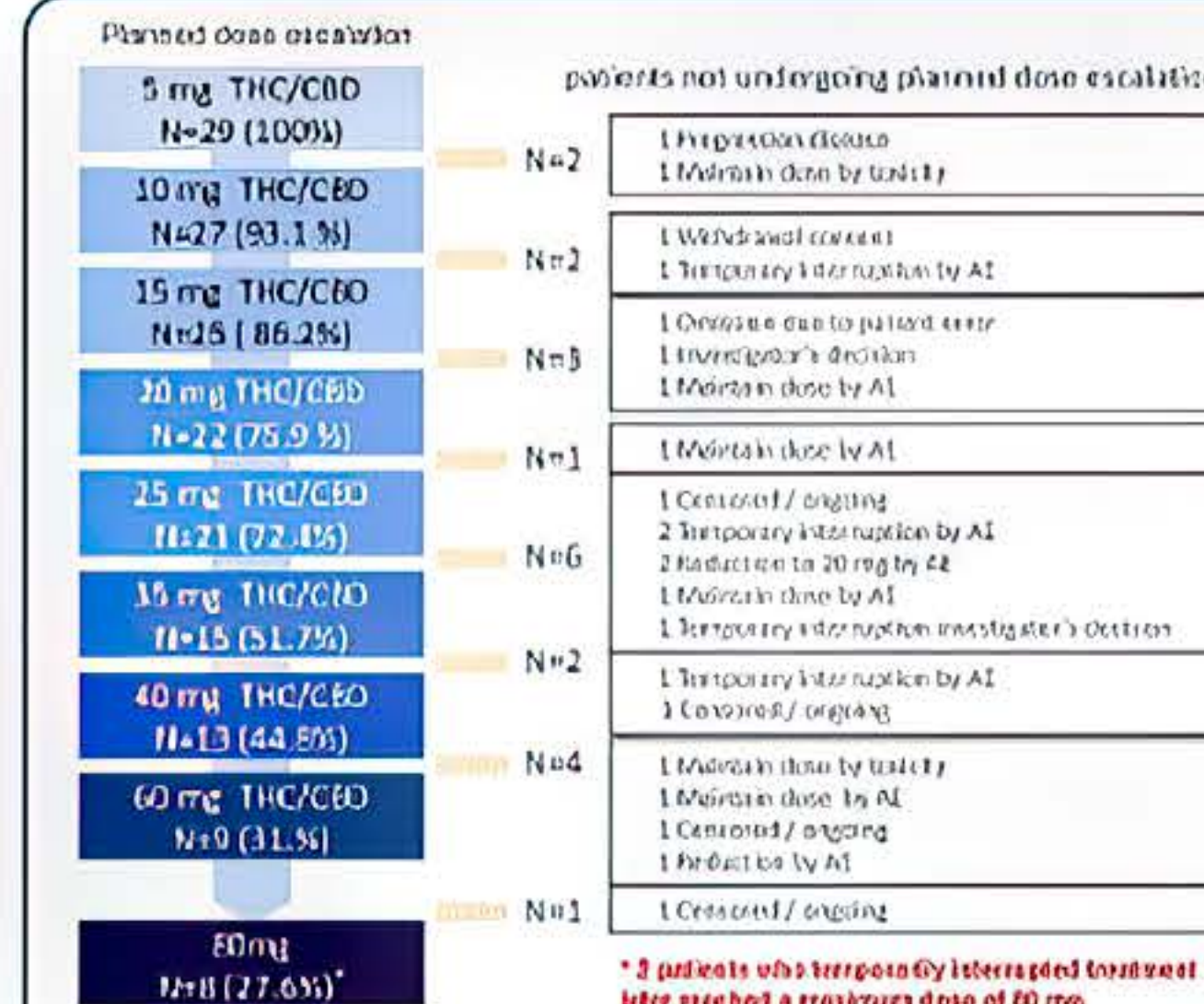
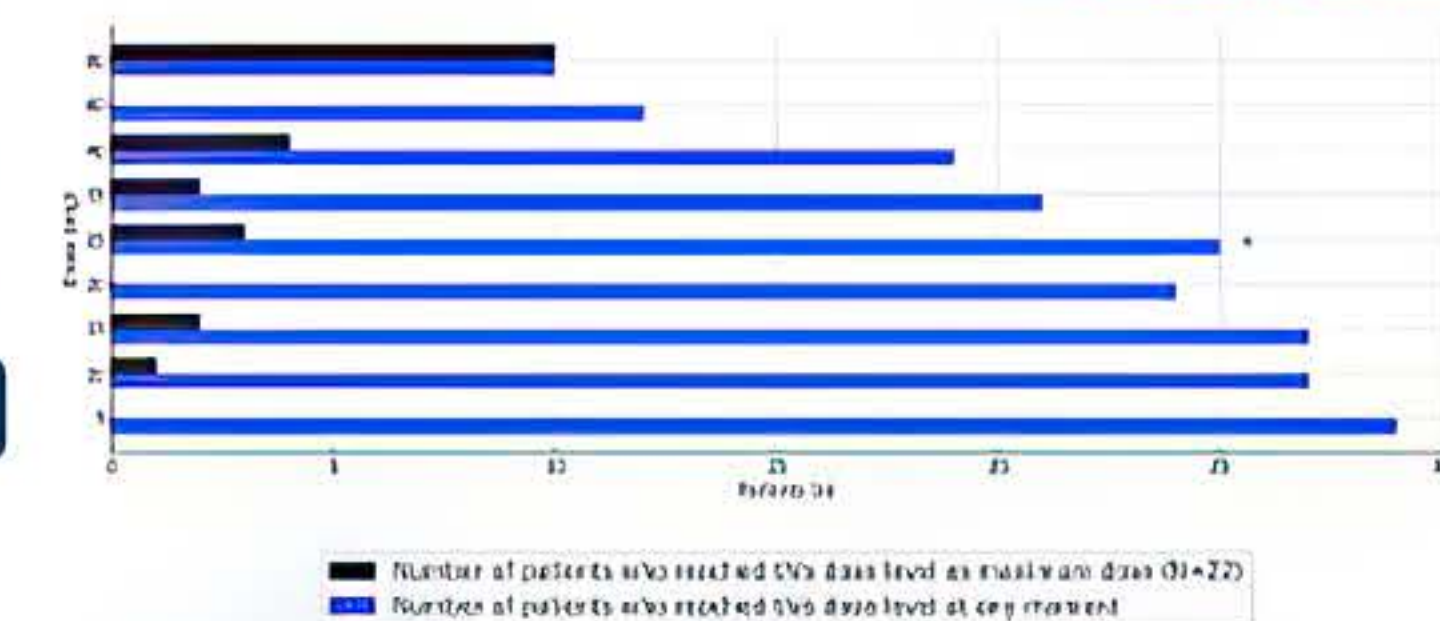


Figure 3. Flow chart showing the patient dose escalation with THC / CBD according to protocol planned dose escalation



*One patient went directly from 15 mg to 25 mg without going through 20 mg.
Figure 4. Maximum THC/CBD doses achieved independently of drug delays and interruptions. Number of patients who reached each dose level at any moment.

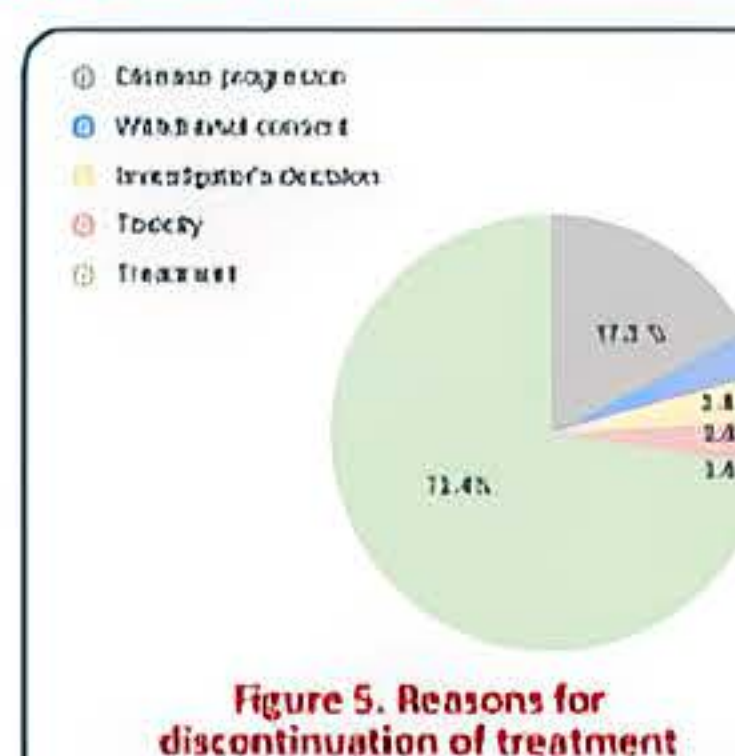


Figure 5. Reasons for discontinuation of treatment

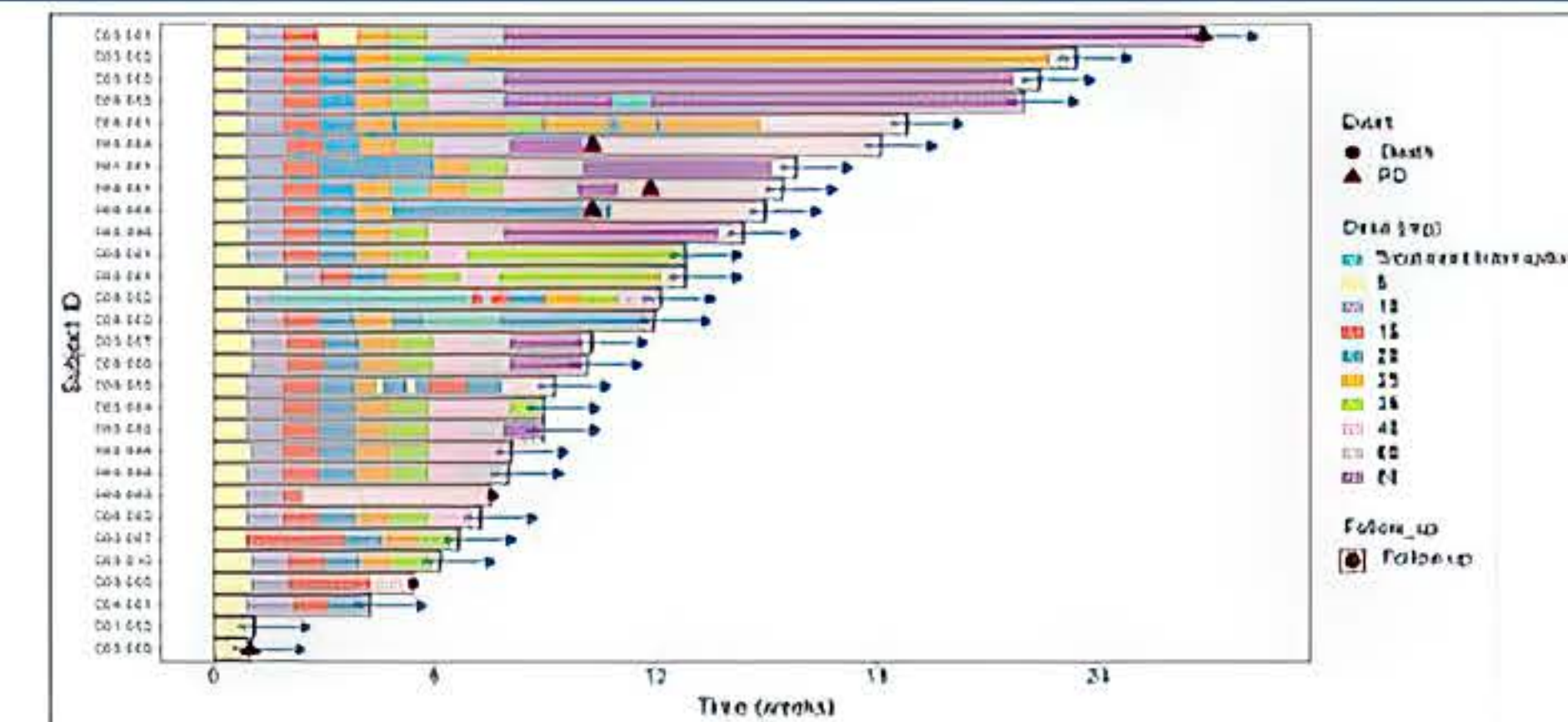


Figure 6. Dose intensity THC/CBD over time

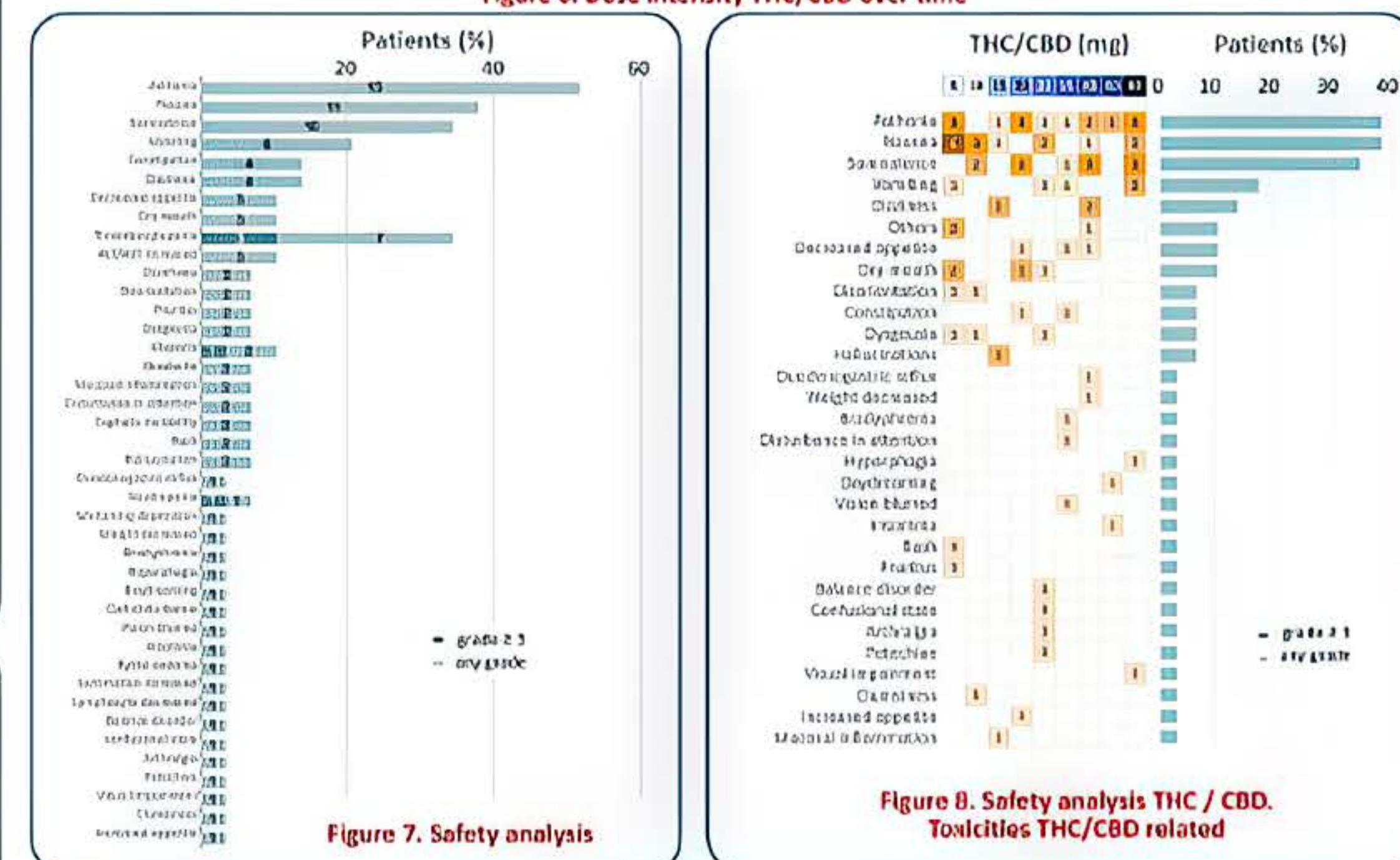


Figure 7. Safety analysis

Figure 8. Safety analysis THC / CBD. Toxicities THC/CBD related

CONCLUSIONS

- Accrual has been completed and THC/CBD oral solution combined with Stupp scheme is being administered safely in patients with GBM.
- Until data cut off 38% patients have reached maximum pre-specified dose of 80 mg with optimal toxicity profile.
- Until data cut off 38% patients have reached maximum pre-specified dose of 80 mg with optimal toxicity profile. The frequency of AEs related to THC/CBD was not clearly dependent on the dose.