A bioequivalence study of a novel liquid and ready-to-use temozolomide oral suspension and temozolomide capsules in patients with primary central nervous system malignancies

Francois Ducray[1], Carole Ramirez[2], Marie Robert[3], Maxime Fontanilles[4], Charlotte Bronnimann[5], Olivier L. Chinot[6], Florian Estrade[7], Xavier Durando[8], Jeremy Bastid[9], Hugues Bienaymé[9], Caroline Lemarchand[9]

1: Service de Neuro-oncologie, Hôpital Neurologique, Hospices Civils de Lyon, France. 2: Centre Hospitalier Universitaire de Saint-Etienne, France. 3: Institut de Cancerologie de l'Ouest, Medical Oncology, Saint Herblain, France. 4: Cancer Centre Henri Becquerel, Rouen, France. 5: Hôpital St André, Bordeaux, France. 6: CHU Hôpital de La Timone, Marseille, France. 7: Centre Eugène Marquis, Rennes, France. 8: Centre Jean Perrin, Clermont-Ferrand, France. 9: ORPHELIA Pharma, Paris, France.

1. BACKGROUND

Oral temozolomide capsule (Temodal®) is approved for the treatment of glioma and glioblastoma in adults and in Europe in children over 3-years

As recommended by international pediatric medical associations, temozolomide is also used for the treatment of high-risk relapsed or refractory neuroblastoma, a solid tumor affecting young children.

Capsules are not adapted to the pediatric population leading caregivers to handle temozolomide capsules, which bears major risks (i.e. dose inaccuracy, temozolomide instability and exposure to cytotoxic drug).

To overcome this situation, the first suspension of temozolomide (Kimozo®) was developed by ORPHELIA Pharma.

The aim of this phase I study was to demonstrate bioequivalence between Kimozo® and temozolomide capsules (Temodal®) and to assess the general and local safety in adult patients.

2. OBJECTIVES

Primary objective

- Demonstrate bioequivalence between Kimozo® oral suspension and Temodal® capsules

Secondary objectives

- Define pharmacokinetic parameters of Kimozo®
- Evaluate the buccal safety of Kimozo®

3. MATERIAL & METHODS

Study design [1]

- Open label, randomized, two-way crossover, single dose bioequivalence study conducted in 8 centers.
- 30 male/female adult patients with primary CNS malignancies and treated with 200 mg/m² temozolomide as monotherapy.
- Patients to receive, under fasting conditions, a single oral administration of Kimozo® oral suspension or Temodal® 100 mg capsules on day 1 and 2 (period 1 and 2) according to randomization.
- Out of the scope of the protocol, from day 3 to 5, patients to receive their usual dose of Temodal® to reach the total dose of 1000 mg/m² for a 5-day cycle.
- A total of 28, 6 mL-blood samples drawn per patient (14 per period): pre-dose (T0) and 10min, 20min, 30min, 45min, 1h, 1h30, 2h, 2h30min, 3h, 4h, 6h, 8h and 10h hours post-dose.

Primary evaluation criteria:

- Pharmacokinetic parameters determined from temozolomide plasma concentrations:
  - C_{max} and AUC_{0-t}

Secondary evaluation criteria

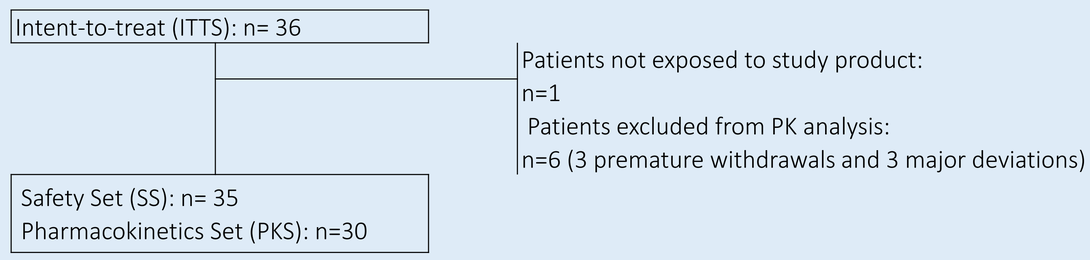
- Pharmacokinetic parameters determined from temozolomide plasma concentrations:
  - AUC_{0-inf}, t_{max}, λ, $t_{1/2}$ and residual area of temozolomide
- Safety parameters: physical examination, including buccal examination, vital signs, adverse events, concomitant treatments, ECG and laboratory examinations.

[1] Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98, rev 1 (August 2010), Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (FDA – Draft September 2013).

4. RESULTS

Population

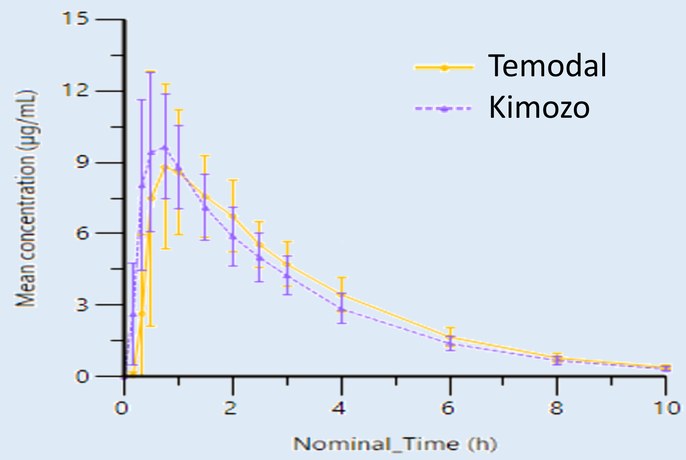
36 patients (male and female) included in 7 sites in France, to reach 30 evaluated patients



In the ITTS population (N = 36):

- 25% were female and 75% were male.
- Age ranged from 20 to 79 years with a mean of 52.3 ± 14.8 years.
- BMI ranged from 19.8 to 30.6 kg/m² with a mean of 24.8 ± 2.9 kg/m².
- Karnofsky score ranged from 60 to 100 with a mean of 85.3 ± 11.3.

Pharmacokinetic analysis and bioequivalence



Pharmacokinetic parameters (n=30)	90% C.I.		Test/Ref. Ratio of Geometric Means (%)	Intra-Patient % CV
	Lower	Upper		
Ln(AUCt)	95.05	99.35	97.18	0.25%
Ln(Cmax)	98.07	118.09	107.62	4.47%

Table 1: Statistical analysis was conducted using Phoenix WinNonlin software (Version 8.1 Pharsight) for all patients who completed the study and who were not excluded due to deviations impacting the pharmacokinetic analysis (i.e. 30 patients of the PKS population).

Safety

- 7/35 (20%) patients reported the occurrence of 9 adverse events. All occurred after treatment initiation (treatment emergent adverse event, TEAE):
  - 4 TEAEs experienced by 3 patients after Temodal®
  - 5 TEAEs experienced by 4 patients after Kimozo®
- No serious adverse events (SAE) reported.
- All TEAEs (lymphopenia, thrombocytopenia, diarrhoea, nausea, headache) most mild in intensity, were resolved before the end of study.
- Vital signs, ECGs and physical findings showed no trends or clinically relevant changes.
- No sign of buccal toxicity (AESI) was reported.

5. CONCLUSIONS

Kimozo®, oral suspension of temozolomide, and Temodal® capsules are bioequivalent

- The results satisfied the bioequivalence criteria of the Bioequivalence Guidelines (90% CI between 80.00% and 125.00%).
- Kimozo® was well tolerated with no sign of buccal toxicity.

SPONSOR: ORPHELIA Pharma, 85 Blvd Saint-Michel, 75005 Paris.
Contact: +33 (0)1 42 77 08 18 - Email: contact@orphelia-pharma.eu