## Supplementary material

# Persistent prevention of oxaliplatin-induced peripheral neuropathy using calmangafodipir (PledOx®): A placebo-controlled randomized phase II study (PLIANT)

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## Appendix 1.

Oxaliplatin Sanofi Specific grade 0-4 Scale (OSSS) for oxaliplatin-related paresthesias/dysesthesias in advanced colorectal cancer

|  |  |
| --- | --- |
| Grade 0 | No symptoms |
| Grade 1 | Paresthesias/dysesthesias of short duration that resolve and do not interfere with function |
| Grade 2 | Paresthesias/dysesthesias, interfering with function, but not activities of daily living |
| Grade 3 | Paresthesias/dysesthesiaswith pain or with functional impairment that also interfere with daily living |
| Grade 4 | Persistent paresthesias/ dysesthesias that are disabling or life-threatening |

## Appendix 1, continued

**Leonard scale**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Upper Extremity Symptoms** | | | If you had symptoms during the last cycle… | | | | | | | | | |
| Do you have… | | | How much symptoms did you have?  Hardly any 🡪 Very much | | | | | Did the symptoms affect your daily activities?  Hardly at all bothered 🡪 Extremely bothered | | | | |
| Tingling (pins and needles) | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Numbness | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Difficulty telling the difference between rough and smooth surfaces | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Difficulty feeling hot things | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Difficulty feeling cold things | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| A greater than normal sense of touch (i.e. putting on gloves) | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Burning pain or discomfort without  cold | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Burning pain or discomfort with cold | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Difficulty identifying objects in your hand (i.e. coin) | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Do you have involuntary hand movements | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Lower Extremity Symptoms** | | | If you had symptoms during the last cycle… | | | | | | | | | |
| Do you have… | | | How much symptoms did you have?  Hardly any 🡪 Very much | | | | | Did the symptoms affect your daily activities?  Hardly at all bothered 🡪 Extremely bothered | | | | |
| Tingling (pins and needles) | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Numbness | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Difficulty telling the difference between rough and smooth surfaces | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Difficulty feeling hot things | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Difficulty feeling cold things | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| A greater than normal sense of touch (i.e. discomfort with socks) | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Burning pain or discomfort without cold | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Burning pain or discomfort with cold | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Legs feel heavy | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Oral/facial Symptoms** | | | If you had symptoms during the last cycle… | | | | | | | | | |
| Do you have…. | | | How much symptoms did you have?  Hardly any 🡪 Very much | | | | | Did the symptoms affect your daily activities?  Hardly at all bothered 🡪 Extremely bothered | | | | |
| Jaw pain | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Eyelids dropping | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Throat discomfort | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Ear pain | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Tingling in mouth | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Difficulty with speech | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Burning pain or discomfort of your eyes | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Loss of any vision | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Feeling shock/pain down back | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Problems with breathing | Yes | No | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |

The average sum of how much symptoms the patients had in Tingling, Numbness and Burning pain or Discomfort with cold in Upper and Lower extremities prior to start of therapy, prior to each new cycle during treatment and prior to the evaluations during follow-up 3, 6, 9 and 12 months after last treatment with chemotherapy were used. These symptoms were rated the highest by the patients. The impact of these symptoms on daily activities mirrored the symptoms scores or were slightly lower in amplitude (data mot illustrated).

## Appendix 2.

PK assessment and analyses of manganese and zinc concentrations

The disposition of calmangafodipir was studied by measuring the plasma concentrations of Mn (see main manuscript), Zn and fodipir as its metabolites ZnDPDP, ZnDPDM and ZnPLED. For the latter analyses, venous blood samples were collected during the first cycle at 6 time points (pre-infusion, immediately after infusion (0 min), 15 min, 30 min, 1 h and 4 h post-infusion). The between treatment arms comparisons regarding changes from baseline in the mean blood levels were done using the ANOVA model with treatment as a fixed factor in the model.

Results

Total plasma zinc concentration dropped slightly immediately after PledOx® infusion with a subsequent increase above baseline already 15 minutes post infusion (Figure 1, Appendix 1). The peak concentration, likely reflecting a redistribution of tissue-stored Zn, was observed at 30 min post infusion in the 5 μmol/kg group. By four hours post infusion, the Zn levels were back to baseline levels. Overall, these data showing a minor and transient decrease followed by an increase in plasma Zn after the dose of 5 μmol/kg suggest that there is limited reason to monitor Zn levels in forthcoming clinical studies.With regard to fodipir and related metabolites, only a few patients had enough quantifiable ZnDPMP and ZnDPDP concentrations to enable a PK analysis (see Figure 2, Appendix 1). This rapid dephosphorylation is not unexpected since similar observations have been made with mangafodipir and in preclinical studies with calmangafodipir. For ZnPLED, the median elimination half-life was approximately 2 hours. Tmax appears shortly after the end of infusion (around 0.3 hours), as expected. Median AUCs and Cmax’s are roughly proportional to dose.

Figure 1 Appendix 2. Plasma concentration-time curve of Zn in the indicated dose groups in the PLIANT study



Figure 2 Appendix 2. Plasma concentration time profile of the respective zinc metabolites ZnPLED, ZnDPMP and ZnDPDP at the doses indicated of calmangafodipirused in the PLIANT study

