# Predicting the placebo response in OA to improve the precision of the treatment effect estimation.

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## Introduction and Motivation

In OA randomized clinical trials (RCTs), the magnitude and the variability of the placebo response negatively impacts the ability to demonstrate superiority of active compounds compared to placebo.

To solve this issue, Tools4Patient has developed a machine learning-based model that predicts the placebo response in chronic pain diseases.

The main objective of this analysis was to assess the performance and applicability of the Placebell©™ placebo response model in a phase 2 trial conducted by UNITY Biotechnology.

## Study Designs and Patients

This clinical trial was a randomized, double-blind, placebo-controlled, single-dose, parallel-group study to assess the efficacy, safety, and tolerability of a single-dose IA administration of UBX0101 in patients with moderate to severe painful knee OA (NCT04129944).

**Study groups:**
Approximately 180 patients were randomized (1:1:1:1) to one of four treatment groups. The four treatment groups were enrolled concurrently :

- Group 1: Placebo
- Group 2: UBX0101 0.5 mg
- Group 3: UBX0101 2.0 mg
- Group 4: UBX0101 4.0 mg

**Study drug:**
The study drug was administered as a single 8 mL IA injection at Week 0, Day 1.

**Endpoints:**
Change from baseline to Week 12 of the WOMAC-Pain, WOMAC-Physical func., Average Pain Score (APS), WOMAC-Stiffness, PGA.

**Baseline data:**

- Psychological questionnaire assessing their personality;
- Baseline disease intensity measure (WOMAC, APS, PGA);
- Demographics and medical history.

## Modeling the placebo response

**Training data:**
Individual data from 211 placebo patients from previous Tools4Patient studies with:

- osteoarthritis of the knee and hip
- peripheral neuropathic pain

The placebo response was measured as the change from baseline of the weekly APS.

**Modeling:**
The placebo response was modeled as linear combination of the baseline patient's data learned with a Gaussian Process with a linear kernel.

This model was prospectively defined before the UNITY trial.

## Predictive Results

The predictive performance evaluated while comparing the predicted placebo response and the actual observed response.

Table 1: Performance of the Placebell©™ covariate to predict the primary and secondary endpoints using baseline data on the Per-Protocol population.

| Endpoints | N | Pearson's correlation Estimate | 95% CI | P-value | R-squared |
|---|---|---|---|---|---|
| Womac-Pain | 173 | 52.6% | [40.9 , 62.6] | <0.001 | 27.7% |
| Womac-Phys | 173 | 47.1% | [34.6 , 57.9] | <0.001 | 22.2% |
| APS | 170 | 39.9% | [26.4 , 51.8] | <0.001 | 15.9% |
| Womac-Stiff | 173 | 55.4% | [44.1 , 64.9] | <0.001 | 30.7% |
| PGA | 173 | 49.2% | [37.0 , 59.7] | <0.001 | 24.2% |

## Placebell©™ adjusted treatment effect

The model predictions were used as a covariate in an ANCOVA to adjust the treatment effect for the placebo response.

The Placebell©™ adjustment increased by 40% the treatment effect precision.

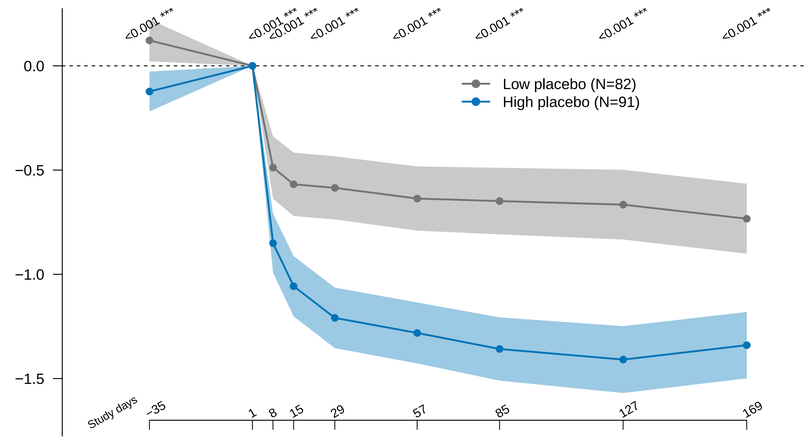
In particular, the model explained some of the treatment groups' differences by slight imbalances in placebo response.

## Model prediction

To further demonstrate the performance of the placebo prediction, the model was used to split patients between high and low placebo responders.

- Low Placebo: Below average predicted placebo response.
- High Placebo: Above average predicted placebo response.

Figure 1 represents the change from baseline of the WOMAC-Pain (Mean and 95% CI) for high and low responders.




## Conclusion

Tools4Patient has developed a machine learning model able to predict the placebo response in chronic pain RCTs.

This model, named Placebell©™ , was used in a phase II, randomized clinical trial conducted by UNITY Biotechnology investigating the effect of an intra-articular injection in approximately 180 patients suffering from painful osteoarthritis of the knee.

The model predictions were highly significant for all study primary and secondary endpoint (p<0.001). Placebell©™ explained 27.7% of the WOMAC-Pain variance on Per-Protocol population.

These results demonstrate usability and performance of Tools4Patient's placebo response model improving the study precision by 40%.