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# The Use of a Multi-modal Pain Test Battery in Early Phase Clinical Drug Development

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# Introduction

- The requirement for pharmacodynamic (PD) measurements in Ph1 studies remains in the pain field
  - to increase confidence in dose selection
  - to increase probability of success in Ph2

- Multiple methodologies exist in Ph1 to measure PD outcomes but
  - choice of model is not clear for any given mechanism
  - pharmacological validation is poor

- The PainCart represents a robust and reproducible, pharmacologically validated tool to demonstrate PKPD in a Ph1 setting using multiple endpoints

# Does the drug hit the target and elicit a response

## The 'Three Pillars of Survival'

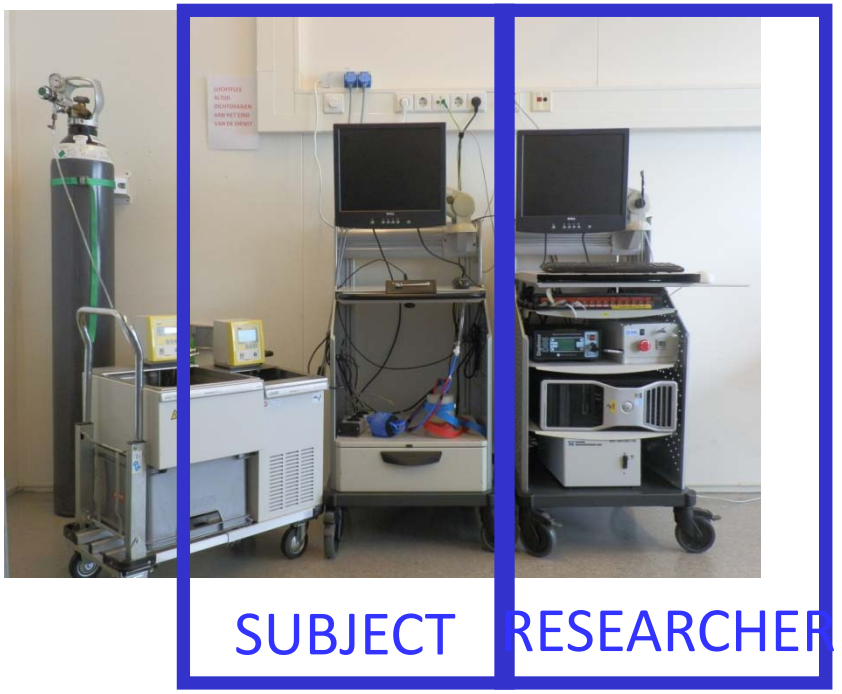
- **Pillar 1:**
  Drug exposure at the target site of action is necessary to elicit a pharmacological effect over a desired time period.
- **Pillar 2:**
  Target occupancy is a prerequisite for expression of pharmacology and target modulation.
- **Pillar 3:**
  Functional modulation of the target is a prerequisite for expression of pharmacological activity to test the mechanism.


Pfizer's framework to help determine three key elements that raise the likelihood of an NME surviving Ph2 testing and moving to Ph3

Drug Discov Today. 2012 May;17(9-10):419-24. doi: 10.1016/j.drudis.2011.12.020. Epub 2011 Dec 29.

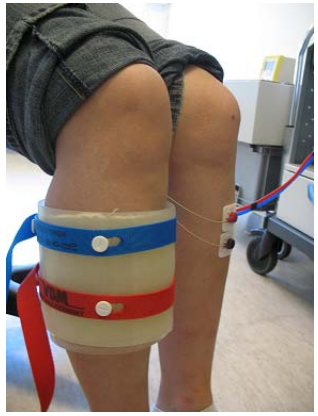
# PainCart - a multiparameter, quantitative, Ph1 compatible platform

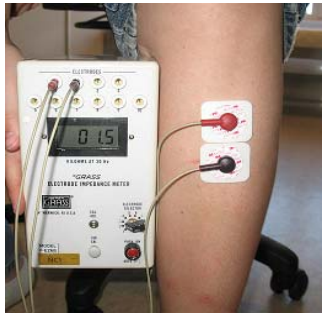
- CHDR developed a "-Cart" concept for neurological and pain testing
- Rapid, multifunctional, automated data capture systems for PKPD assessments in early development
- PainCart is deigned to investigate
  - Different modalities of pain Different physiologies (cutaneous and muscle pain, descending pathways)



# A variety of stimuli, covering major c-fibre classes are incorporated

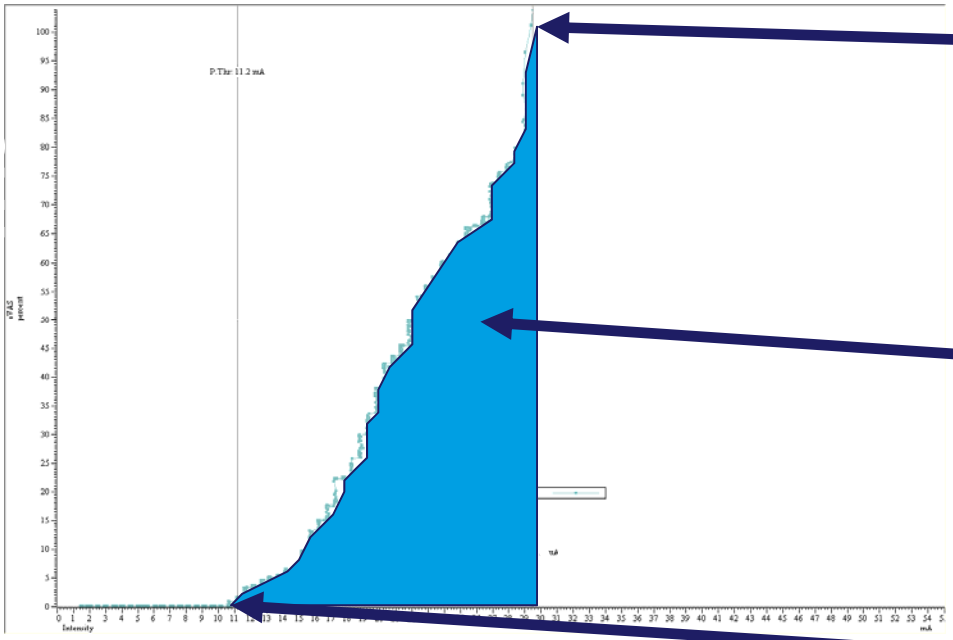
- Electrical Stimulation
  - Staircase
  - Burst
- Pneumatic Pressure
- Cold Pressor
- Conditioned Pain Modulation
- Thermal stimulation
  - Medoc TSA-II 30Thermode
- UVB model






# Endpoints

- Stimulus-Response function
  - Subjects comparable at all stimulus intensities
  - Area Under the Curve

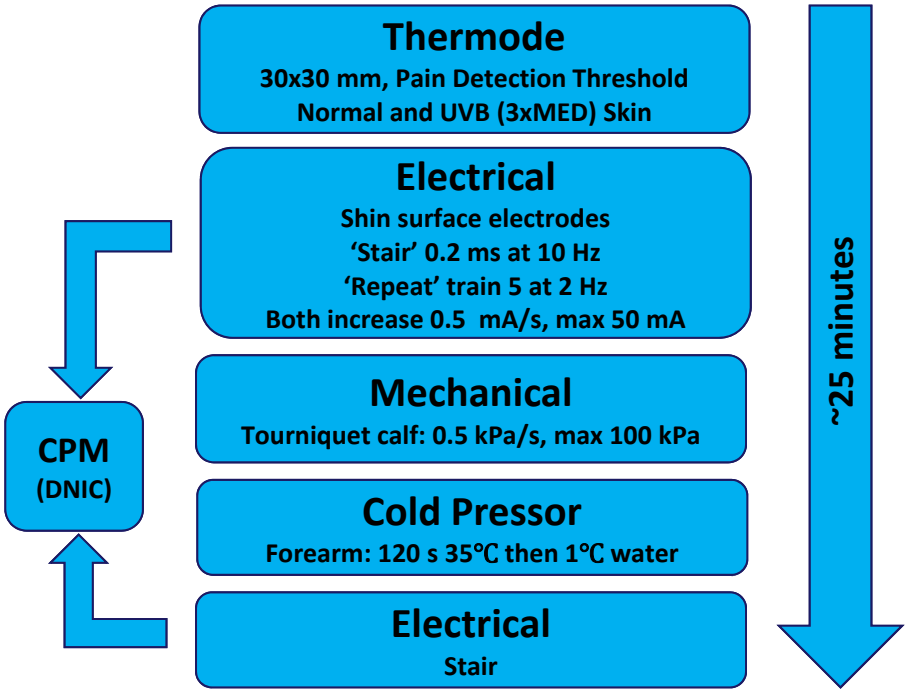



Pain Tolerance Threshold (VAS=100)

AUC (VAS x time)

Pain Detection Threshold (VAS=1)

# PainCart® Validation: Study Design




**PK & PD each visit:**
**0 (x2), 0.5, 1, 2, 3, 4, 6, 8 and 10 hrs**

**4 visits with 1 week washout**
**Randomised, double-blind, placebo-controlled**

**IV dosing (n=16)**
Fentanyl 3 µg/kg
S-Ketamine 10 mg
Phenytoin 300 mg
Placebo

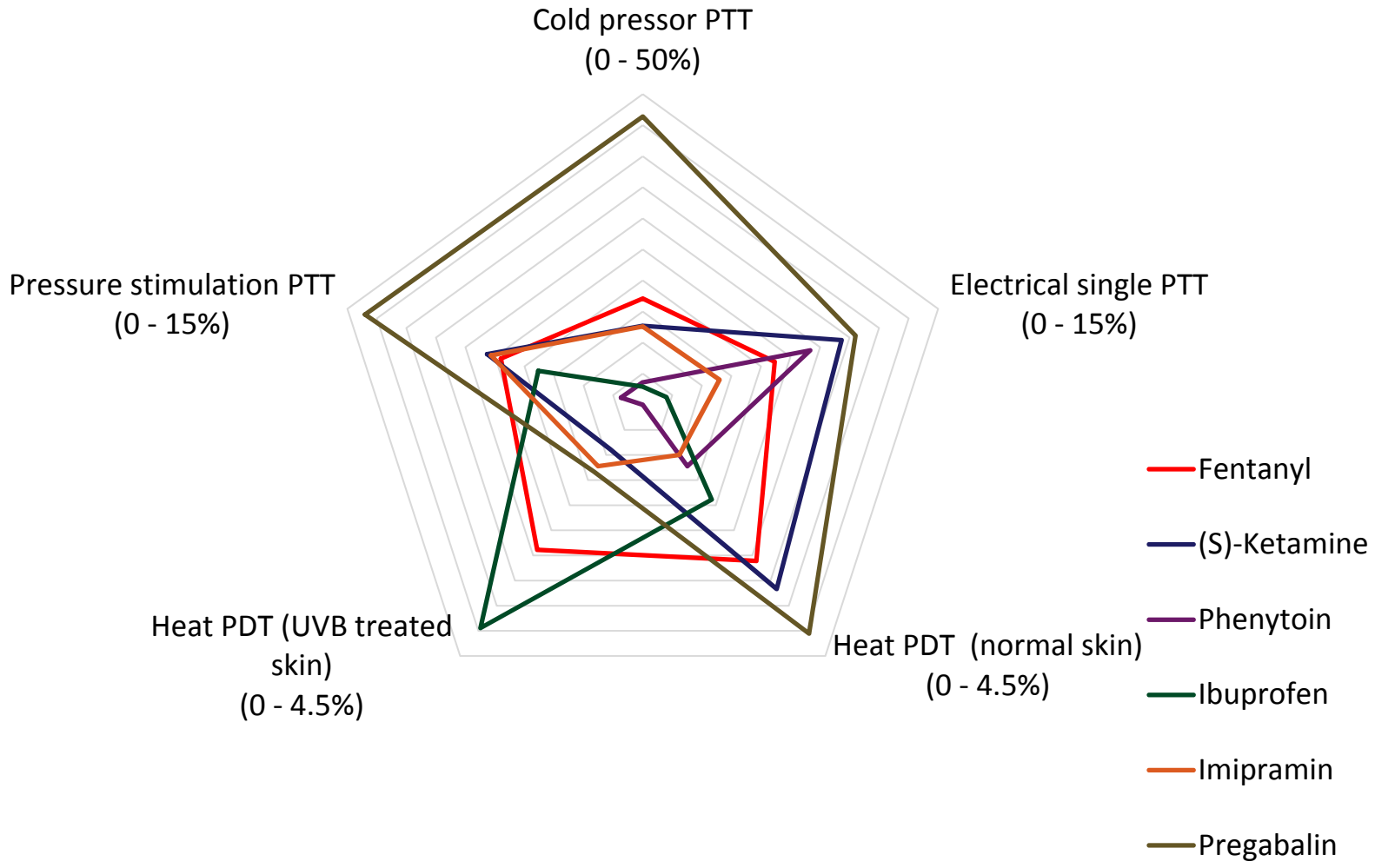
**Oral dosing (n=16)**
Ibuprofen 600 mg
Imipramine 100 mg
Pregabalin 300 mg
Placebo

# PainCart® Validation Study: **Overview**

| PTT | Ketamine | Fentanyl | Phenytoin | Ibuprofen | Pregabalin | Imipramine |
|---|---|---|---|---|---|---|
| Half Life | 15 mins | 3.5 h | 10-15 h | 3 h | 6 h | 8-20 h |
| Analysis | 0-1 h | 0-5 h | 0-10 h | 0-5 h | 0-5 h | 0-10h |
| Thermal Grill* | | | | | | |
| Thermode – Normal Skin | | | | | | |
| Thermode – UVB treated | | +1hr PDT | | | | |
| Electrical - Single | | | +PDT | | | |
| Electrical - Repeat | +AUC | | | +AUC | | |
| Pressure | | +1hr PTT | | | | |
| Cold Pressor | +AAC | +1hr PTT | | | +PDT/ +AAC | |
| iCPM (Electrical Stair) | | | | | +PDT | +PDT |

*Unpleasantness AUC. GREEN – P<0.05. YELLOW – P<0.10. GREY– NS vs. placebo. +indicates other related parameter P<0.05 vs. placebo.

# PainCart® : **Unique profile per analgesic drug**



# The paradigm under evaluation

- Move rapidly to early development
- Use PainCart to inform investment into Ph2
- Spend less preclinical resources in generating non-translational in vivo data

**Multiple divergent mechanisms**

- Subtype selective $Na_v$ 1.7 blocker
- GABA partial agonist
- Selective TrkA kinase inhibitor

**In parallel investments**

PainCart in Ph1

Patient efficacy studies for all 3 mechanisms

**Anticipated Outcomes**

PainCart enabled proof of pharmacology and confidence in dose selection

PainCart predicted efficacy?

# Status of individual assets at the time of PainCart execution

| Mechanism / compound | Indication | Status at time of PainCart proposal | Clinical trials .gov link | Aim of PainCart |
|---|---|---|---|---|
| **Nav 1.7 PF-05089771** | Acute and chronic pain | Completed dental pain study, IEM study, ongoing chronic pain study | https://clinicaltrials.gov/ct2/results?term=PF-05089771&Search=Search | •Dose selection (inform PKPD)<br>•Efficacy prediction |
| **$GABA_A$ modulator PF-06372865** | Chronic lower back pain | Completed Ph1, PET, PD studies | https://clinicaltrials.gov/ct2/results?term=PF-06372865&Search=Search | •Dose selection (inform PKPD)<br>•Efficacy prediction |
| **Trk A kinase inhibitor PF-06273340** | Nociceptive pain | Ongoing in Ph1 SAD and MAD | https://clinicaltrials.gov/ct2/results?term=PF-06273340&Search=Search | •Dose selection (inform PKPD)<br>•Efficacy prediction |

# Study designs for mechanisms under evaluation

**B7431003 (GABA)**

- 4-way XO
- N=20
- 15 mg PF-06372865
- 65 mg PF-06372865
- PGB +ve/-ve control

**B5261005 (pan-Trk)**

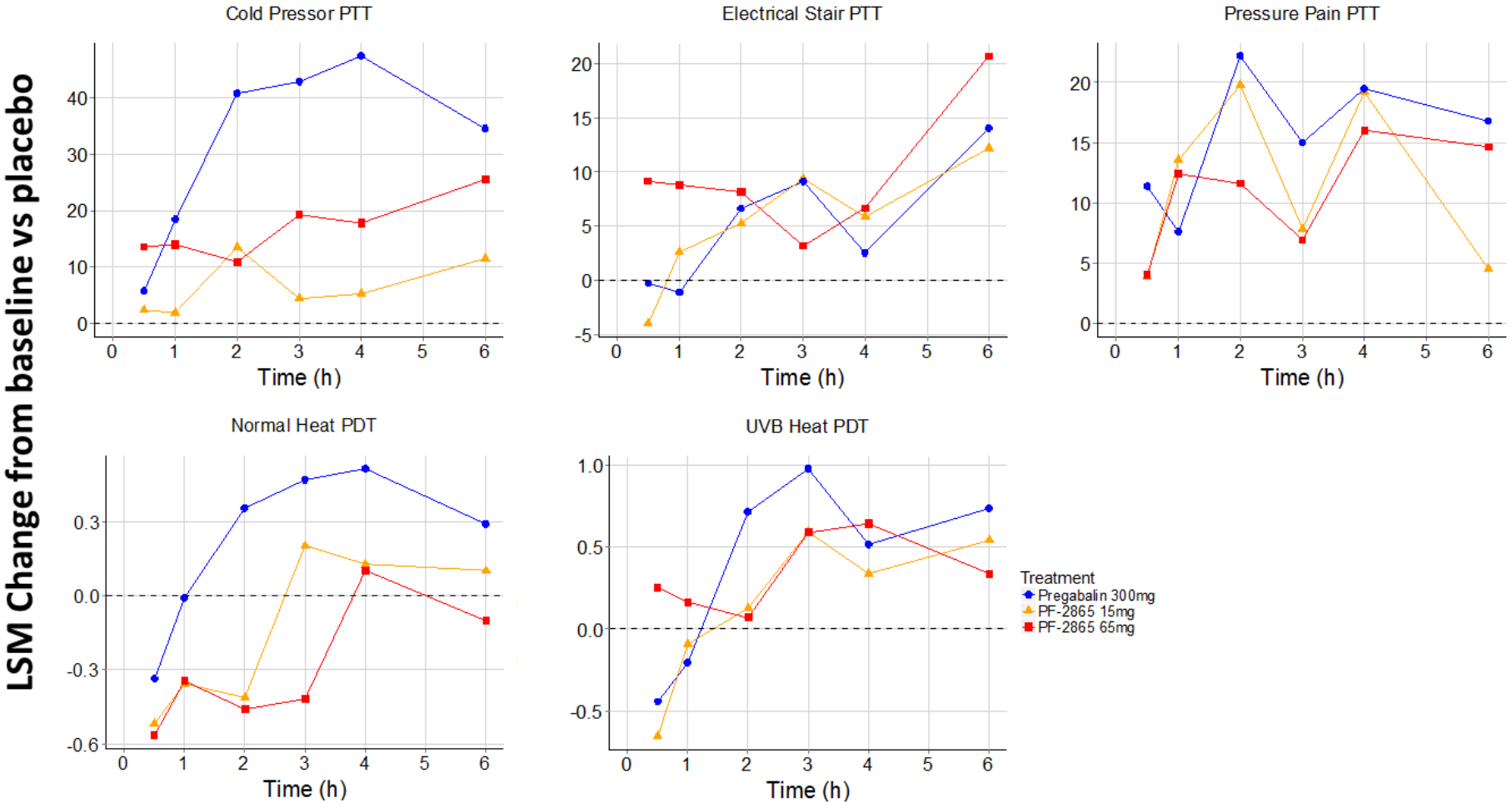
- 5-way XO
- N=20
- 50 mg PF-06273340
- 400 mg PF-06273340
- PGB +ve/-ve control
- IBU +ve/-ve control

**B3291010 ($Na_v$ 1.7)**

- 5-way XO, N=25
- 300 mg PF-05089771
- 300 mg PF-05089771 + 300 mg PGB
- PGB +ve/-ve control
- IBU +ve/-ve control

- Mechanistic hypotheses
  - GABA may resemble PGB – mechanistically both involved in spinal analgesia pathway
  - Pan-Trk should be +ve in sensitise UVB heat endpoint in which NGF has been implicated as a major sensitising mechanism (and negative in others)
  - $Na_v$1.7 showed marginal effect in dental pain, anticipate similar response

# Time courses for PainCart endpoints using GABA modulator and pregabalin versus placebo

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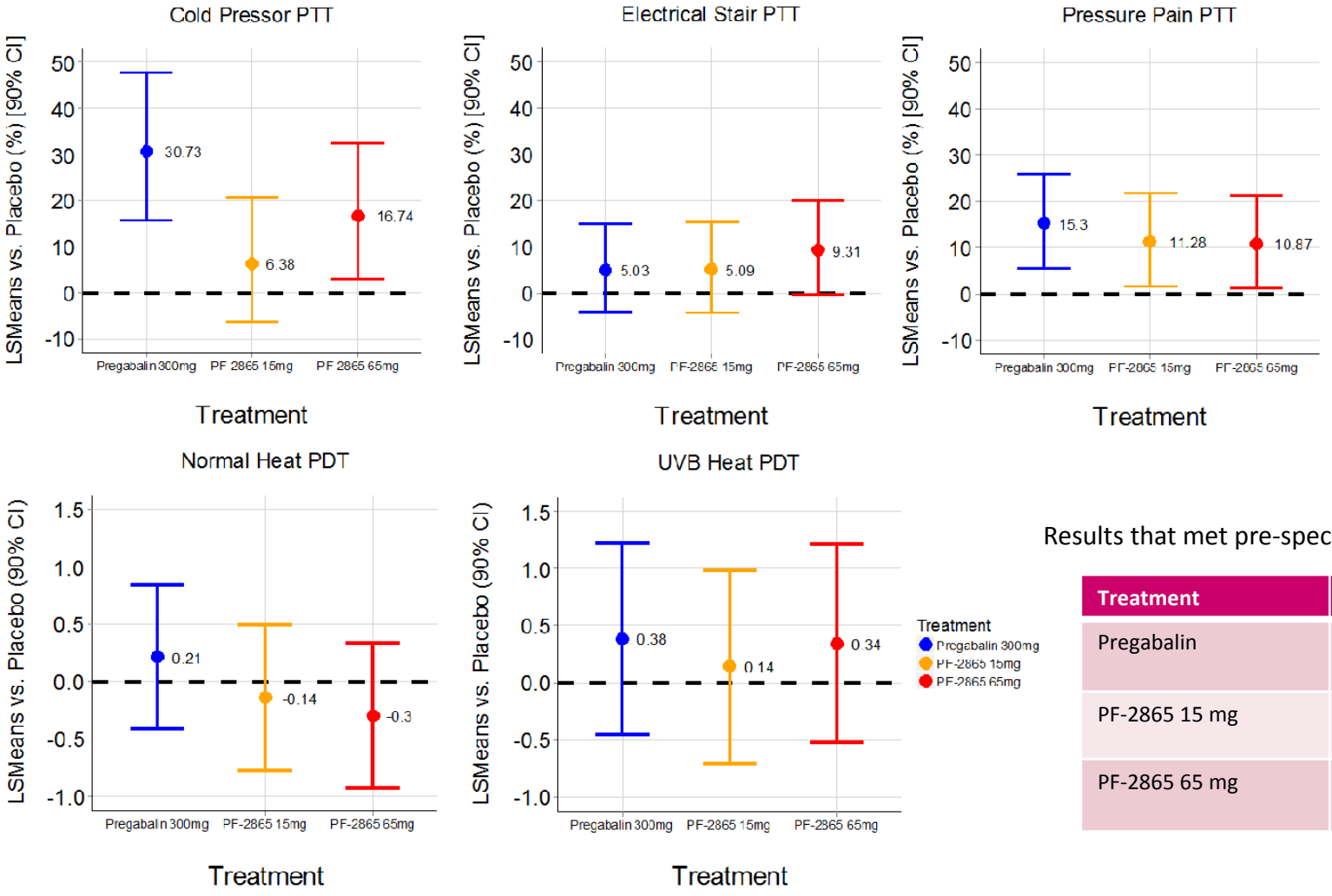
# Summary of results with 15 and 65 mg PF-06372865, and PGB based on primary endpoint ($AUC_{0-6}$ c.f. placebo)




Results that met pre-specified decision criteria:*

| Treatment | Endpoint |
|---|---|
| Pregabalin | Cold Pressor PTT, Pressure Pain PTT |
| PF-2865 15 mg | Pressure Pain PTT |
| PF-2865 65 mg | Cold Pressor PTT, Pressure Pain PTT |

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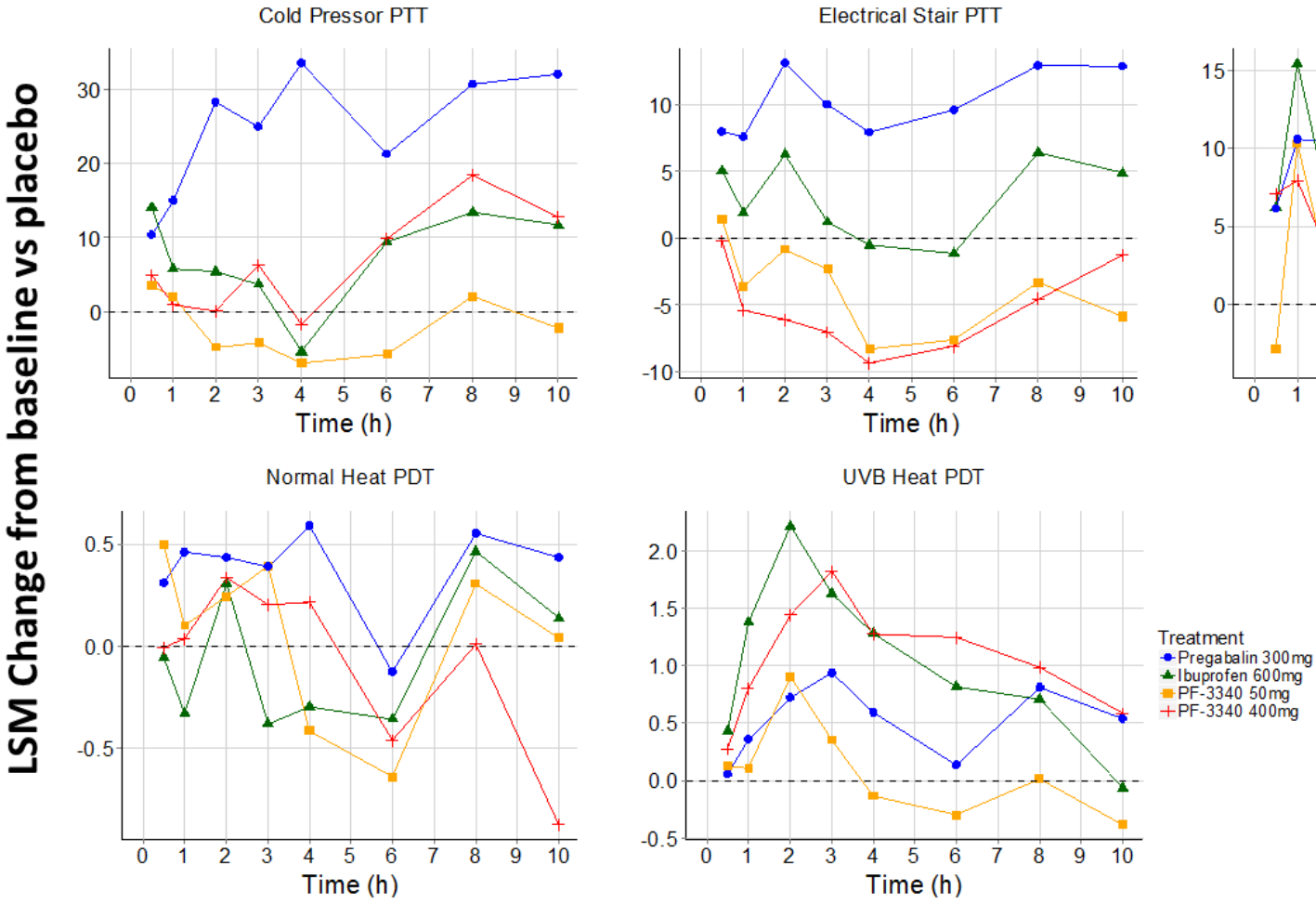
*At least 95% confident effect is greater than placebo

# Summary of results with pan-Trk inhibitor, pregabalin and ibuprofen

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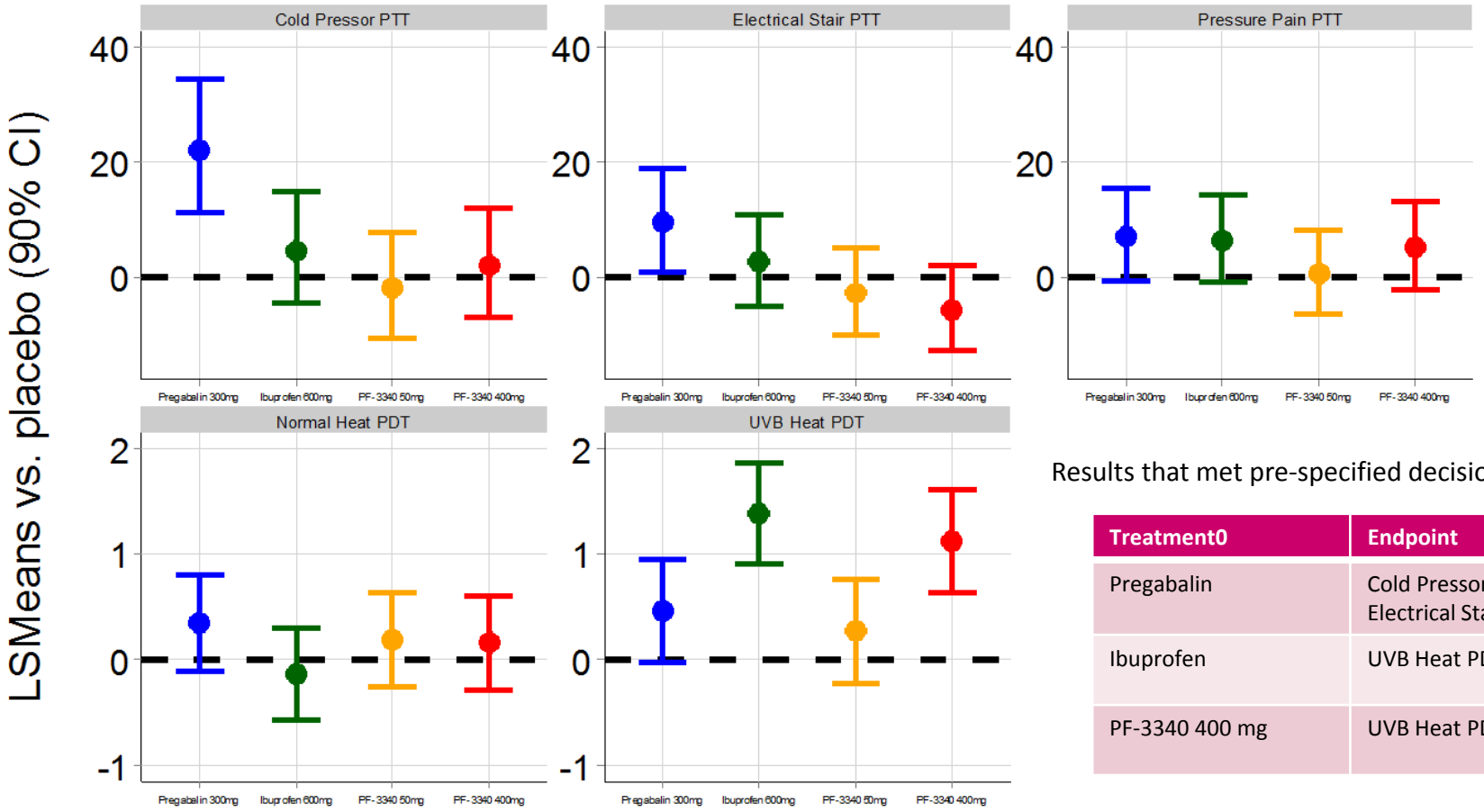
# Summary of results with 50 and 400mg PF-6273340 PGB and IBU based on primary endpoint ($AUC_{0-4}$ c.f. placebo)

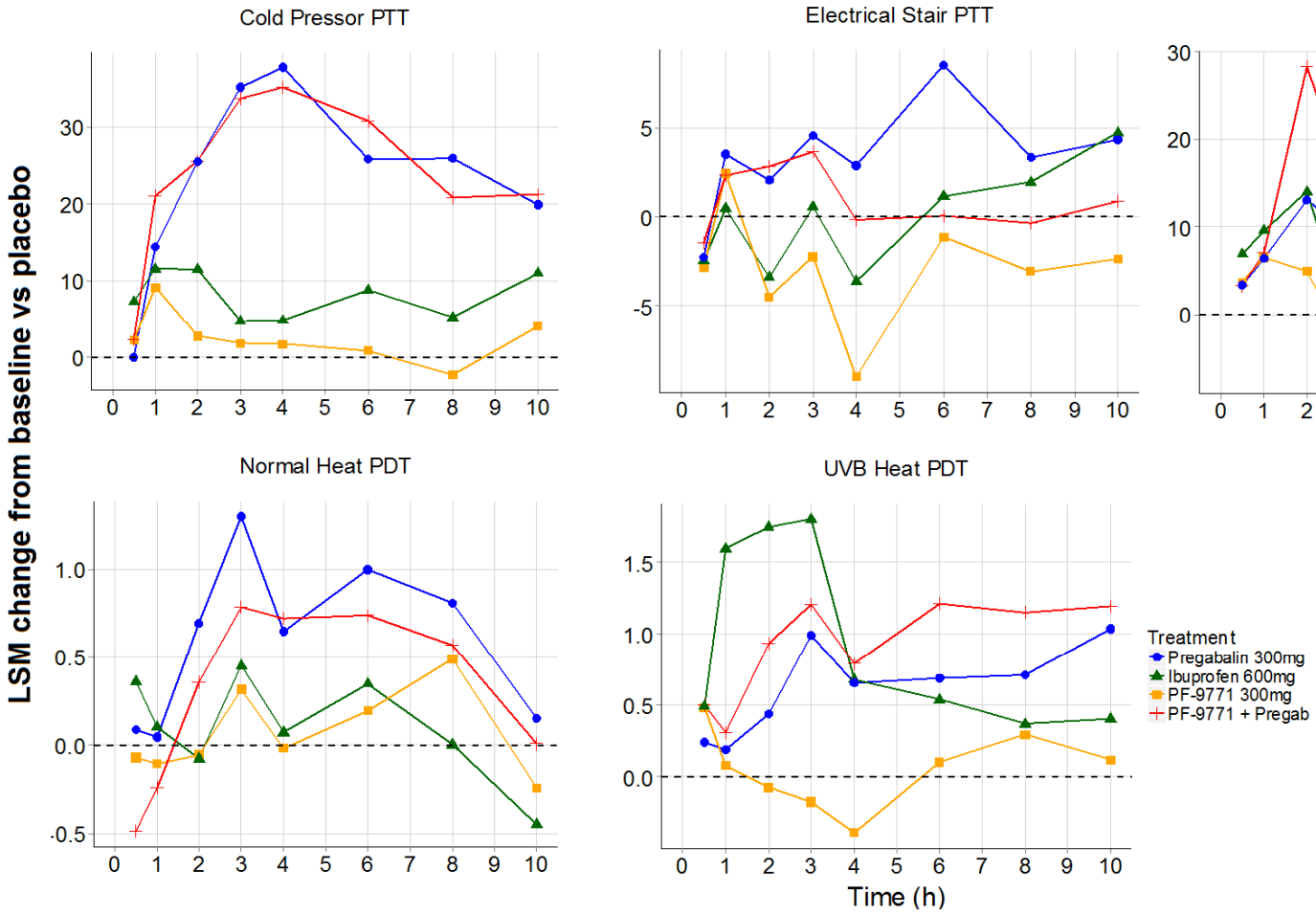



Results that met pre-specified decision criteria:*

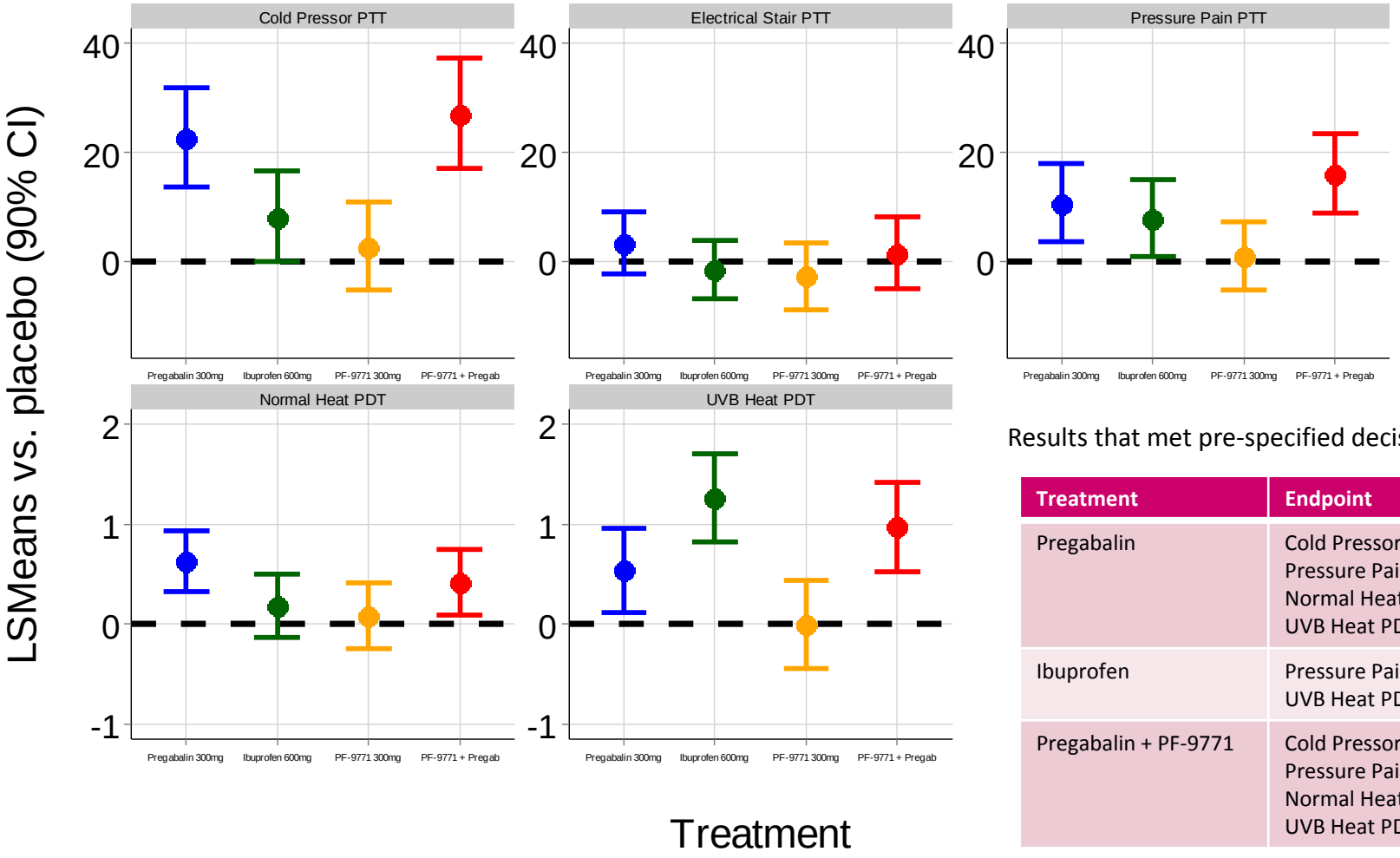
| Treatment0 | Endpoint |
|---|---|
| Pregabalin | Cold Pressor PTT, Electrical Stair PTT |
| Ibuprofen | UVB Heat PDT |
| PF-3340 400 mg | UVB Heat PDT |

*At least 95% confident effect is greater than placebo

# Time courses for Paincart endpoints using $Na_v1.7$ inhibitor alone and in combination with PGB, PGB and IBU



# Summary of results with $Na_v$ 1.7 blocker PF-05089771 based on primary endpoint ($AUC_{0-6}$ c.f. placebo)




Results that met pre-specified decision criteria:*

| Treatment | Endpoint |
|---|---|
| Pregabalin | Cold Pressor PTT, Pressure Pain PTT, Normal Heat PDT, UVB Heat PDT |
| Ibuprofen | Pressure Pain PTT, UVB Heat PDT |
| Pregabalin + PF-9771 | Cold Pressor PTT, Pressure Pain PTT, Normal Heat PDT, UVB Heat PDT |

*At least 95% confident effect is greater than placebo

# Conclusions I

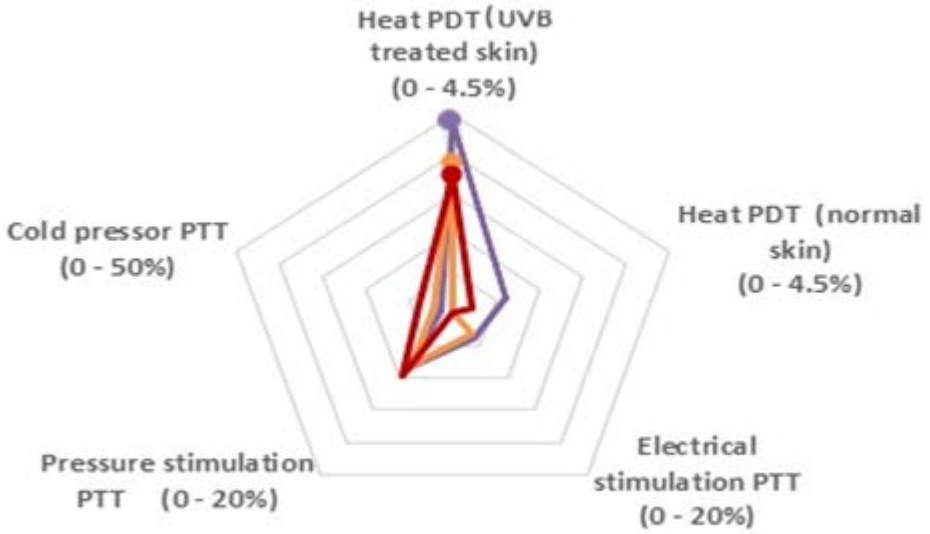
- $Na_v$ 1.7 blocker failed to show a response in PainCart and has demonstrated only modest efficacy in patient studies

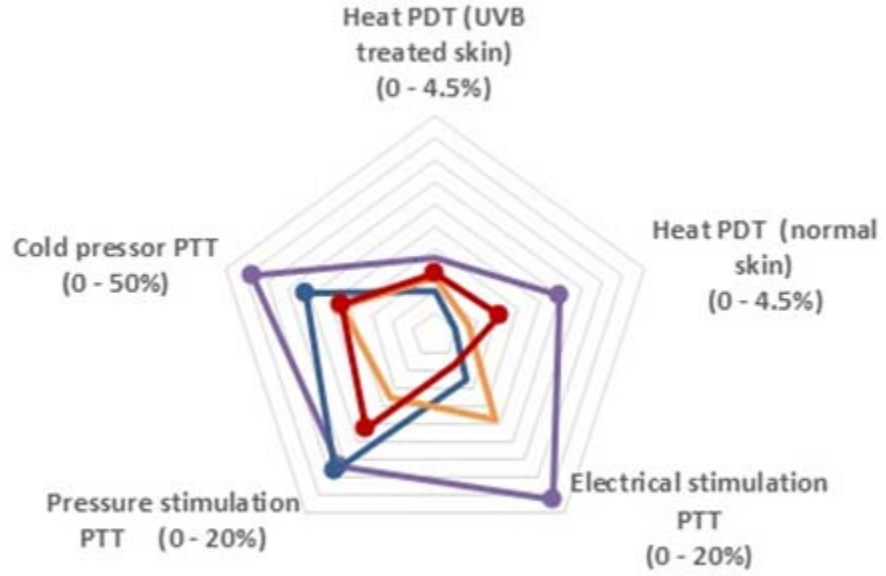
- $GABA_A$ modulator showed robust responses in PainCart, similar to PGB. Should this have been tested in a NeP patient setting?
  - The compound failed in CLBP in patients with no neuropathic component

- Pan Trk kinase inhibitor was only effective in UVB sensitised heat pain, as predicted, and a robust dose/exposure response
  - The compound was not subsequently tested in patients

# PainCart® reproducibility for acute and chronic pain mechanisms

- Ibuprofen reproducibility over 3 independent studies




- Pregabalin reproducibility over 4 independent studies

# Conclusions II

- Positive controls (PGB and IBU) performed highly consistently in different studies over a wide time range

- Different potential analgesic mechanisms clearly impact different pain PD measurements based on their target pathways

# Conclusions III

- The PainCart offers a reliable Ph1, HV assessment for multiple mechanisms and could, with hindsight, have been used
  - to make earlier stop/go decision for the mechanisms studied
  - to help in choice of patient populations

- It remains to be seen if decisions on future development of pain compounds will be influenced prospectively by such PKPD data generated in HV Ph1 studies

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unlocking the true potential