COVID-19 Lockdown Conditions and Depression Assessment Data from an Exploratory Open Label MDD Trial

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Disclosures

- Employee of Praxis Precision Medicines, Inc

Outline

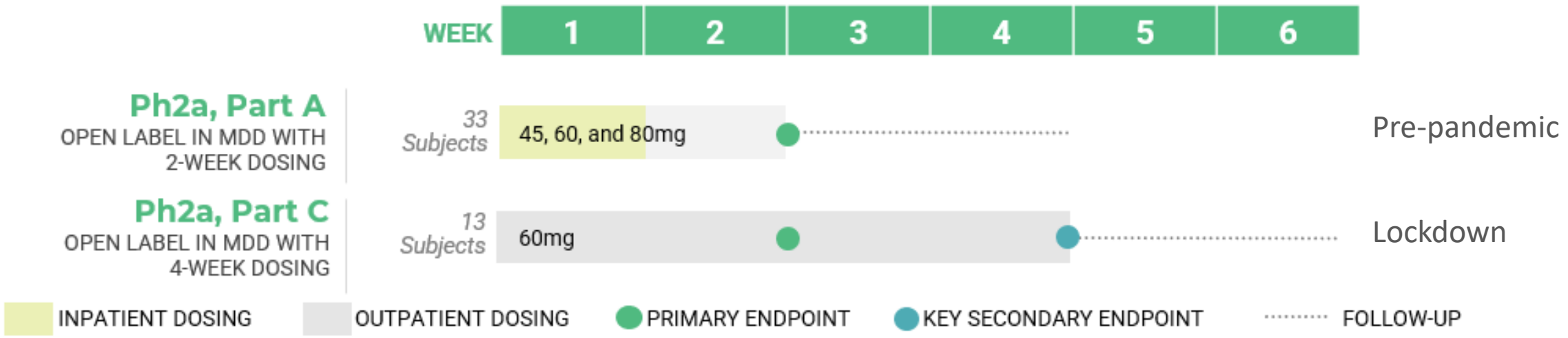
- Background and trial design
- Timeline of trial conduct and COVID-19 pandemic lockdown impacts
- Examination of differences in pre-and post pandemic MDD assessment data*
- Impact on design of subsequent trials

* Presentation focuses on comparative efficacy assessment endpoint findings between trial cohorts; full trial results to be presented at a later date

Background

- Phase 2a MDD trial conducted in Melbourne, Australia from May 2019 to October 2020
  - PRAX-114: a neuroactive steroid $GABA_A$ positive allosteric modulator with preference for extrasynaptic $GABA_A$ receptors in development for Major Depressive Disorder
- Initial 2-week dosing cohorts (Part A) using three fixed dose levels conducted prior to onset of COVID-19 pandemic
- An additional cohort (Part C) with a previously assessed dose level conducted to evaluate 4-week outpatient dosing
- Moderate pandemic restrictions at start of Part C dramatically escalated to be among the most restrictive lockdown conditions globally

PRAX-114 Phase 2a open label safety, tolerability, and efficacy trial in MDD



- Part A objective: evaluate timing and magnitude of treatment effects on HAM-D with 2-weeks PRAX-114 across a range of doses
- Part C objective: evaluate the safety of 28-day outpatient dosing and Day 15 to Day 28 HAM-D treatment effect profile.
- Because first week in Part A was inpatient, analyses for this presentation compared Part A and Part C on the Day 15 outpatient assessments

- Diagnosis of MDD present for ≥ 4-weeks, with a screening HAM-D score of ≥22
- Permitted participants who had demonstrated inadequate response to antidepressant treatment or who had lost a prior response
- Excluded treatment-resistant depression

Registered to anzctr.org.au; ACTRN12619000575134

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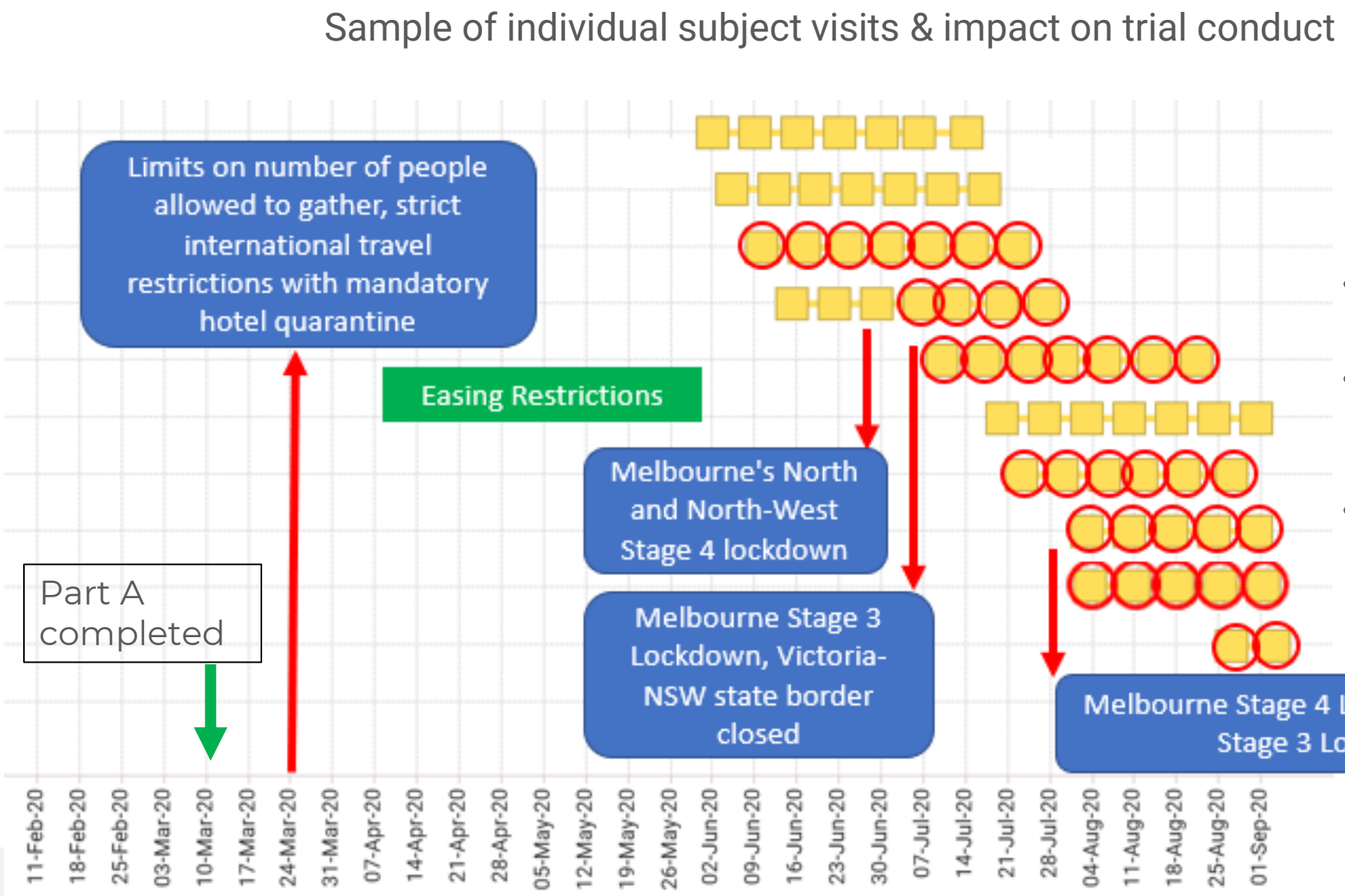
Timeline of Part C visit dates with COVID-19 events and impacts



- Developed COVID-19 risk mitigation guidance, issued mid-April 2020
- Local outbreaks and escalating Lockdowns led to abrupt switch to remote visits at varying time points
- Proactive mitigation and site engagement supported safe and continued conduct of trial

COVID-19 lockdown restrictions in Melbourne during conduct of Part C

- Stage 3 Lockdown:
  - Residents couldn't leave their home except for care or medical reasons, shopping for essentials, work or study that could not be done at home, and exercise
  - Retail stores could remain open subject to social distancing
  - Bars and cafes were takeaway only.
- Stage 4 Lockdown (added to restrictions above):
  - Curfews from 8pm to 5am every evening, retail stores closed (other than essential services).
  - Residents only allowed to leave their house for work and essential health, care or safety reasons, or to purchase food and necessary supplies within a 5km radius from home.
  - Only 1 person per household could leave for essential goods, and only once per day.
  - Permitted to exercise outside once a day for up to 1 hour.
  - Gathering sizes limited to 2.

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Rationale for examining differences in Part A and Part C HAM-D data

Similar baseline characteristics in both cohorts

	Part A 2-week (Inpt/Outpt)	Part C 4-week (Outpt)
	45 mg, 60 mg, 80 mg N=33	60 mg N=13
Insufficient response to antidepressant	79%	77%
Baseline HAM-D	24.9	24.6

- Dosing with PRAX-114 led to a marked improvement in the HAM-D score within two weeks of treatment in all groups.
  - Part A: similar HAM-D treatment effect across all 3 dose levels
  - Similar improvements in secondary efficacy endpoints within both Parts
  - All doses generally well tolerated
  - Part C: Similar treatment effect and safety profile from Day 15-28
- HAM-D improvement at Day 15 approximately 3 points greater in Part A than in Part C

No findings with typical factors that might contribute to differences in Part A and Part C assessment data

- Adherence?
  - No difference in visually-confirmed compliance with treatment between Part A and Part C
- Switch to remote visits/ratings?
  - Australian investigators/staff experienced with telehealth prior to conduct of the study
  - Examination of variability in HAM-D: similar range of standard deviations in HAM-D change from baseline in Part A and Part C
- Participant characteristics?
  - No systematic differences in course of illness, prior treatment response, demographics

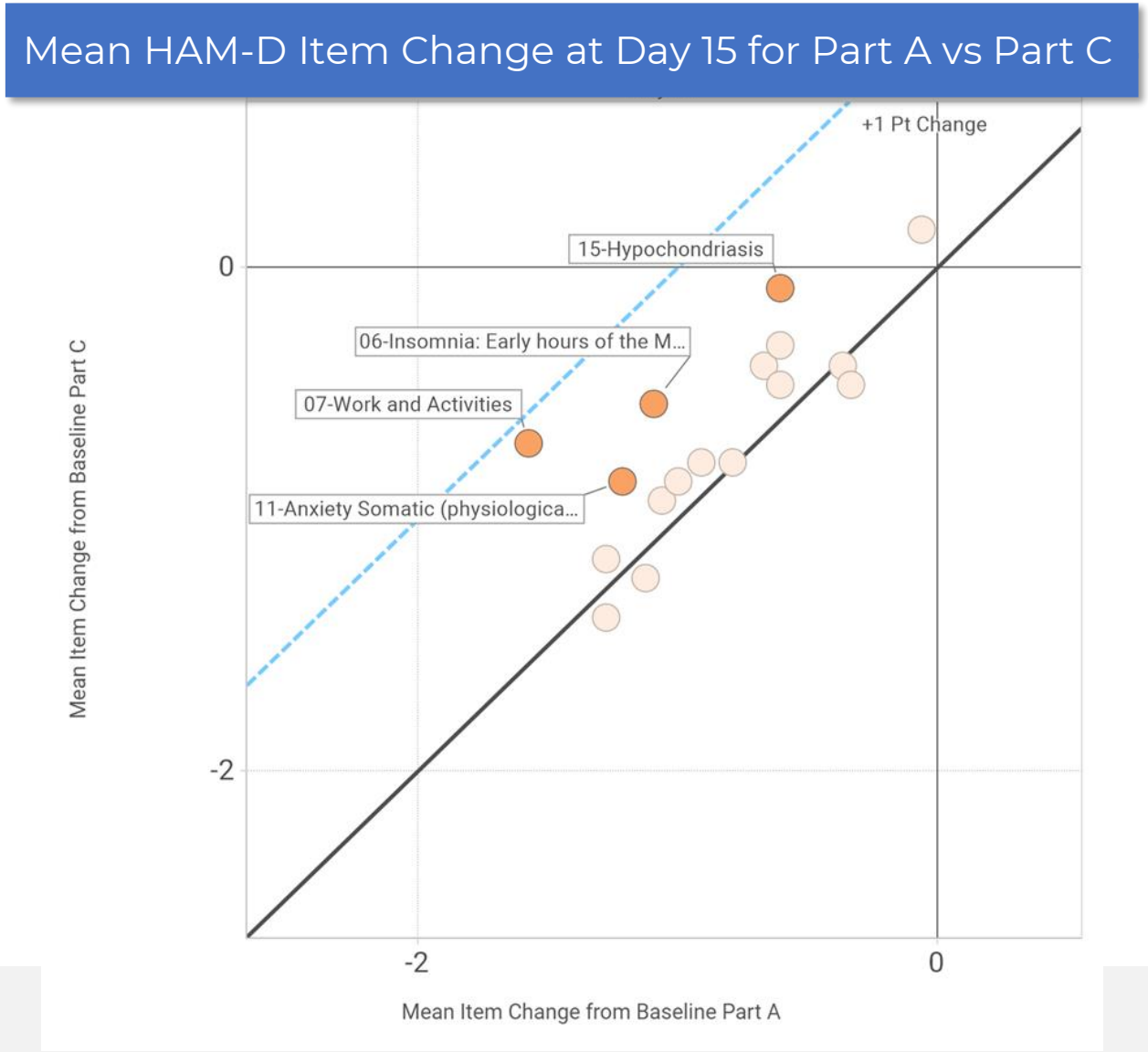
Examination of differences in Part A and Part C assessment data

- HAM-D item-level comparisons
- Participant-reported vs. rater-administered assessment item-level comparisons
- Intra-subject visit to visit variability during active treatment

Part C Day 15 HAM-D item level differences from Part A consistent with limitations of COVID-19 lockdown & environmental stressors

- HAM-D items furthest from diagonal contributed the largest impact on HAM-D Total score differences

- HAM-D items that comprised majority of Part A-Part C difference consistent with potential lockdown impacts:
  - Work and Activities
  - Insomnia: Early Hours
  - Hypochondriasis
  - Anxiety Somatic



HAM-D scale anchors for items demonstrating largest difference in lockdown subjects illustrate rating considerations

COVID-19 Lockdown activity restrictions could impact subject's ability to meet 3 hr. criterion in anchor

7 WORK AND ACTIVITIES

0 |__| No difficulty.
1 |__| Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
2 |__| Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
3 |__| Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
4 |__| Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

HAM-D items potentially susceptible to COVID-19 environmental stressors and health risks

15 HYPOCHONDRIASIS

0 |__| Not present.
1 |__| Self-absorption (bodily).
2 |__| Preoccupation with health.
3 |__| Frequent complaints, requests for help, etc.
4 |__| Hypochondriacal delusions.

6 INSOMNIA: EARLY HOURS OF THE MORNING

0 |__| No difficulty.
1 |__| Waking in early hours of the morning but goes back to sleep.
2 |__| Unable to fall asleep again if he/she gets out of bed.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:

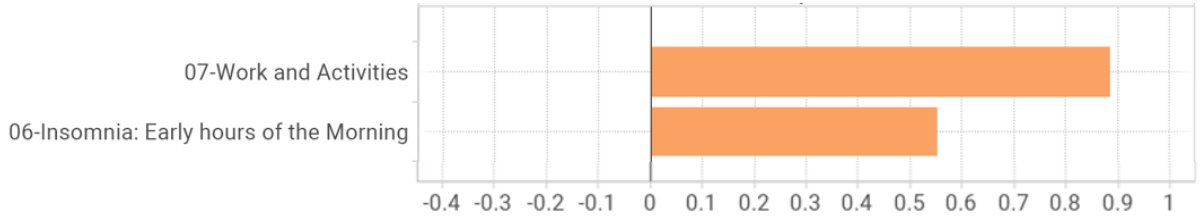
gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing
urinary frequency
sweating

Examination of differences in Part A and Part C assessment data

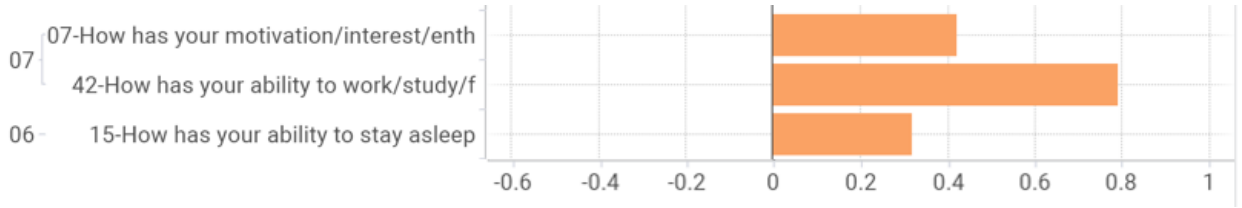
- HAM-D item-level comparison
- Participant-reported vs. rater-administered assessment item-level findings
- Intra-subject visit to visit variability at specific time points

Similarities between HAM-D and participant-reported Symptoms of Depression Questionnaire item level Part A/Part C differences

Ranked HAM-D items by magnitude of change from pre-pandemic to lockdown



Ranked matching SDQ items by magnitude of change from pre-pandemic to lockdown



- SDQ items reflecting HAM-D Work and Activity construct also represented the largest Part A/Part C difference
- No SDQ item that directly measures hypochondriasis
- Somatic Anxiety items of SDQ don't directly correspond to content of the HAM-D item

HAM-D Work and Activities:

- SDQ 7: motivation/interest/enthusiasm
- SDQ 42: ability to work/study/function at home

HAM-D Insomnia-Early

- SDQ: ability to stay asleep around the time before waking up

Examination of differences in Part A and Part C assessment data

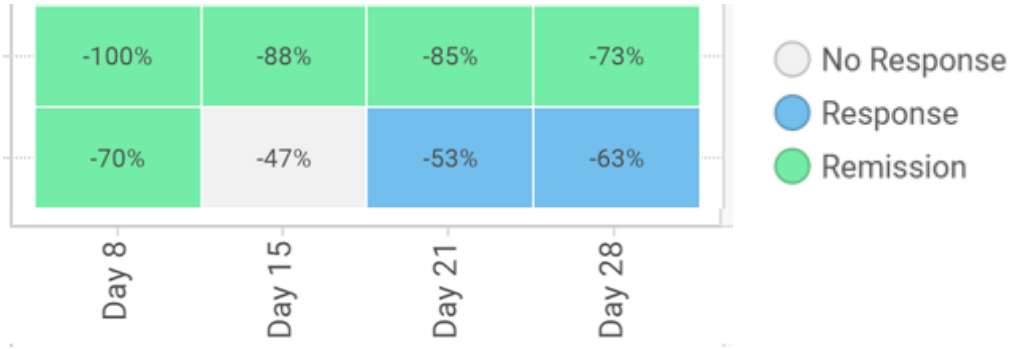
- HAM-D item-level comparison
- Participant-reported vs. rater-administered assessment item-level findings
- Intra-subject visit to visit variability

Intra-subject visit to visit fluctuation during active treatment greater in Part C vs. Part A

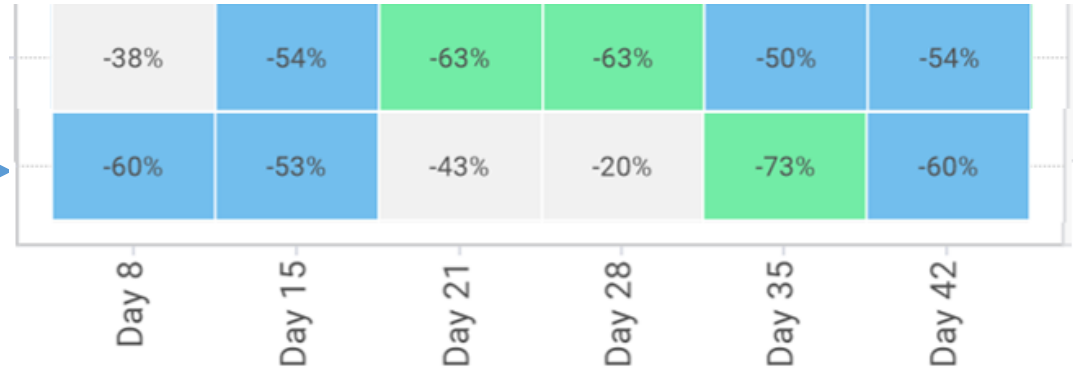
- Visit to visit assessment scores on active treatment typically stable once MDD response is achieved (top row of examples)
- HAM-D fluctuation during active treatment (lost response that later returned) more common in Part C (bottom row)
  - Part A: 2/33 (6 %)
  - Part C: 3/13 (23%)
- Site source documented stressful events related to pandemic lockdown conditions during Part C
  - **Example:** Chef who had opened a restaurant and enrolled in trial just prior to activation of Stage 4 pandemic lockdown restrictions
- Not linked to in-clinic vs. remote assessment patterns

Examples

Part A (2-week treatment):



Part C (4-week treatment):



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Implications for design and conduct of subsequent placebo-controlled trials in MDD

- Included participant reported assessment of perceived stress at baseline and subsequent trial visits for exploratory analyses
- Design features to minimize data variability and impact of pandemic-related events during conduct of trial
  - Incorporated telehealth technology and a fixed telehealth visit
    - Specific rater training for telehealth assessment administration
    - Standardize participant and rater experience across sites
  - Prospective operational processes for management of pandemic public health interventions and individual participant COVID-19 infection management

Conclusions and next steps

- Despite challenging environment, trial conduct was maintained during Melbourne's COVID-19 lockdown, rapid treatment effect of PRAX-114 generally consistent with pre-pandemic cohorts
- Depression assessment data differences in pandemic lockdown cohort appear mostly consistent with expectations for impact of that environment
- Observed efficacy assessment impacts may be less likely to affect outcomes in larger placebo-controlled trials conducted in a broader set of regions
- Experience gained was applied to design and conduct of follow up placebo-controlled trial

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