CONSIDERATIONS & PRACTICES IN MONITORING COVID-19 IMPACT –

an illustrative example

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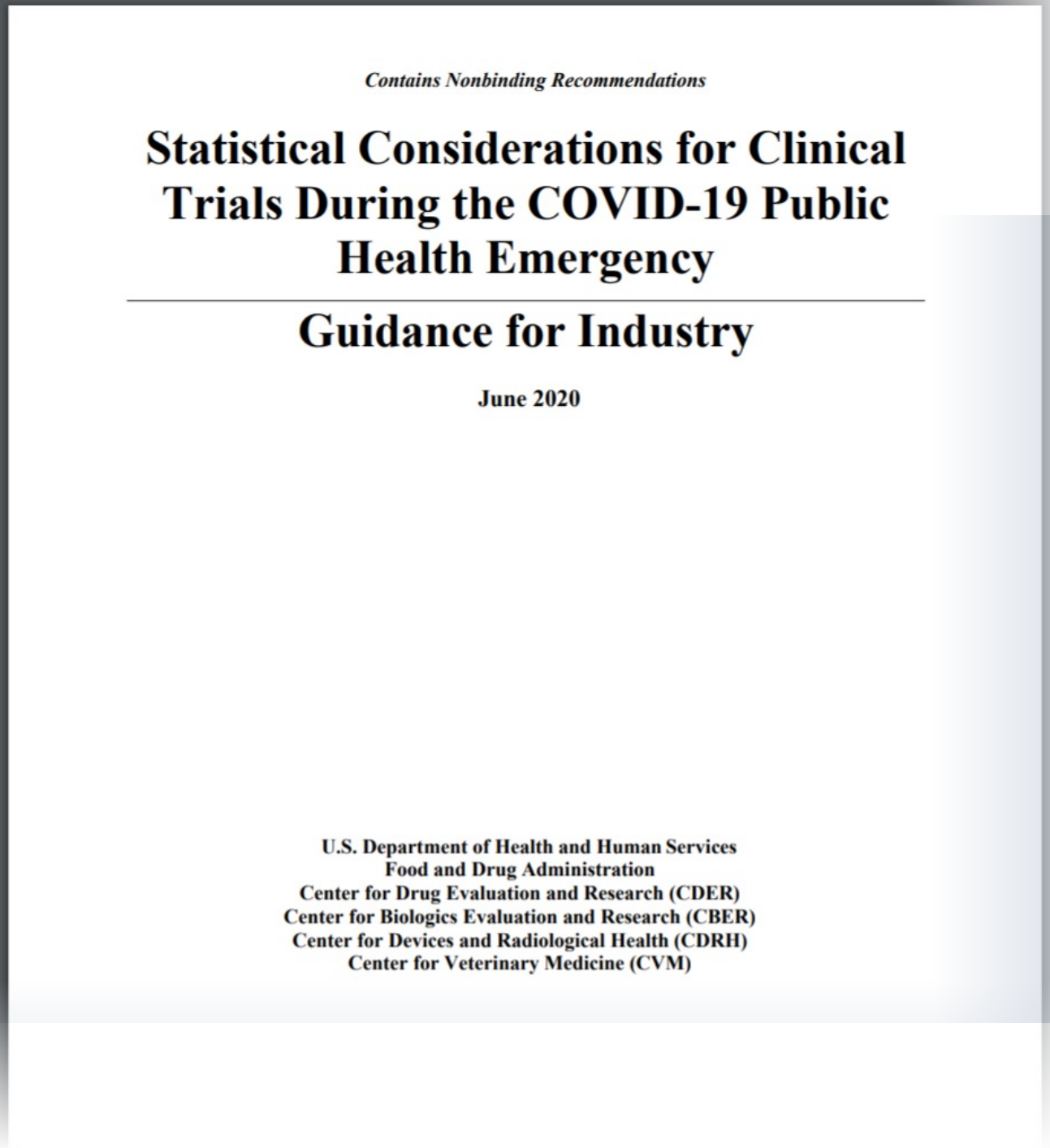
AMGEN®


Contains Nonbinding Recommendations

Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

Guidance for Industry

June 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)

“Sponsors should consider how to approach the analysis of data from participants who are missing endpoint ascertainment or the investigational product was interrupted because of COVID-19…”

COVID-19 POTENTIAL IMPACT ON STUDY

Endpoint Type	Missed both dose & assessment (e.g. pts not going to clinic)	Dose taken, missed assessment (e.g. received treatment, but assessments not performed)	Missed Dose, Assessment taken (e.g. did not receive treatment, but assessments continued)
Clinical Outcome **or** **Patient Reported Outcome (PRO)**	Focus is on proportion of missing visits. If missing is attributed to COVID-19 and proportion of missingness is balanced between groups → MAR assumption	MAR Assumption	**Potential for dilution of treatment effect due to missed dose** Mitigation • provide home delivery of IP • telemedicine • consider alternative estimand or subset excluding subjects identified by baseline information & potentially missing dose due to COVID-19
PRO measured from Daily Diary or Event	N/A – daily data still collected	N/A – daily data still collected	

MAR = Missing At Random

PRESENTATION GOAL

Illustrate how 3 types of plots can help us understand the extent of

a) missed doses

b) missed assessments

c) assessments without expected dosing

Provide useful tips on sorting of information and interactive code options

LATE-PHASE STUDY EXAMPLE

- N ≈ 200 subjects
- Treatment Period: 50 weeks with dosing every other week
- Primary endpoint measured at week 24
  - binary
  - primary analysis: non-responder imputation

Questions:

How much did the coronavirus pandemic affect:

- subjects' receipt of investigational product (IP)?
- subjects' undergoing of disease assessments?
  - power drop acceptable?
- potential observable treatment effect?

ONE WAY TO ANSWER THESE QUESTIONS: TABLES OF NUMBERS

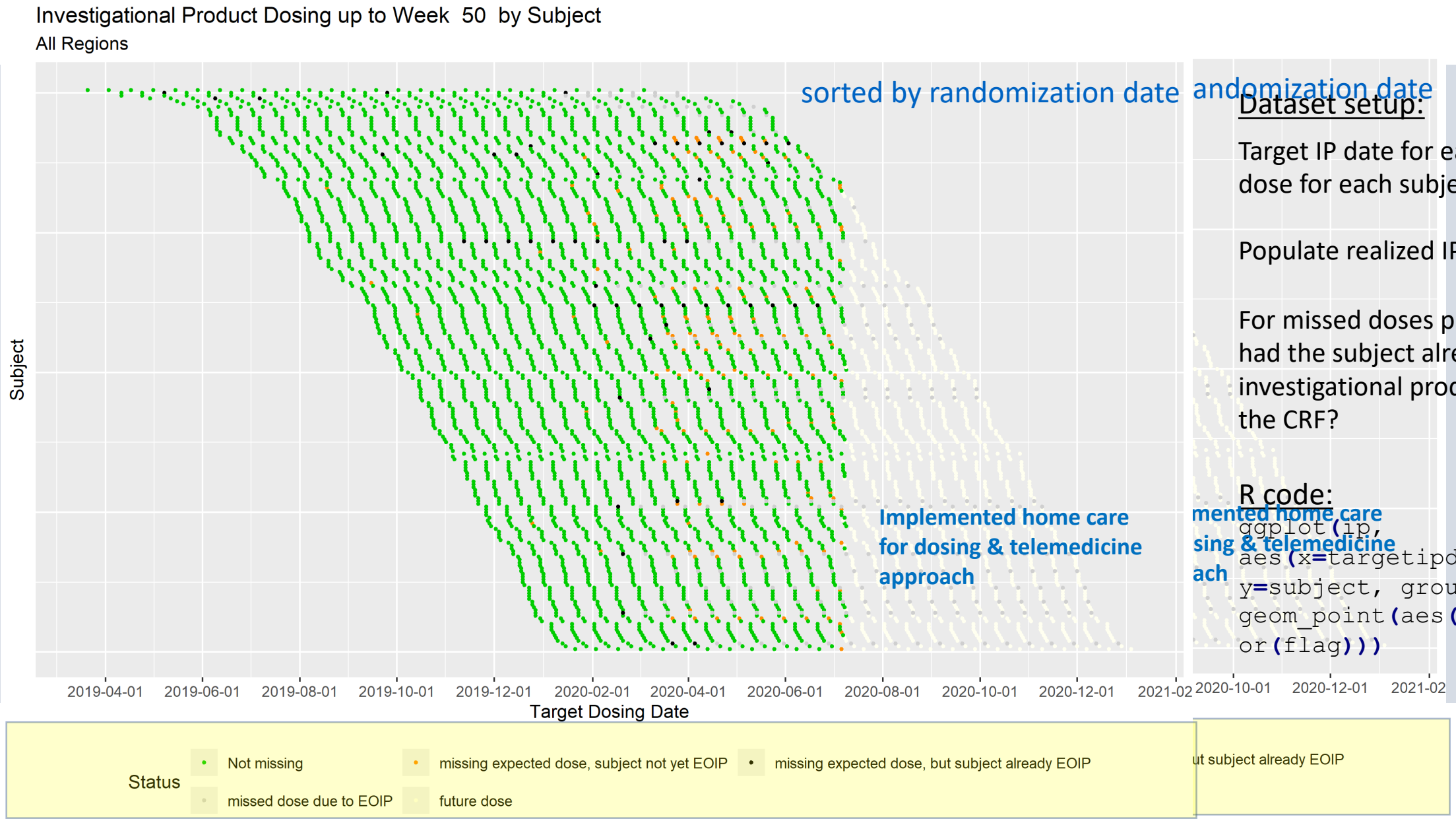
partially

Dosing Week	0	2	4	…	18	20	22	24
Not missing dose	201	200	197	…	184	182	179	178
Missing *expected* dose (target dose date before EOIP date)	0	1	4	…	10	11	14	13
subject still not yet EOIP	0	1	3	…	7	9	9	8
subject now EOIP	0	0	1	…	3	2	5	5
Missing *unexpected* dose (target dose date after subject already EOIP)	0	0	0	…	7	8	8	10
Missed dose yet still came in for next assessment	0	1	4	…	6	8	8	6
Future Dose	0	0	0	…	0	0	0	0

3 PLOT TYPES TO HELP US UNDERSTAND MISSING DOSES & MISSING ASSESSMENTS

1. IP Dosing Plot
2. Assessment Plot
3. IP Dosing + Assessment Plot

FIRST LOOK: GENERAL DOSING PATTERNS



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ut subject already EOIP

Dataset setup:

Target IP date for each scheduled dose for each subject

Populate realized IP dates

For missed doses prior to today(), had the subject already ended investigational product according to the CRF?

R code:

```
ggplot(ip,
aes(x=targetipdate,
y=subject, group=flag)) +
geom_point(aes(color=as.fact
or(flag)))
```

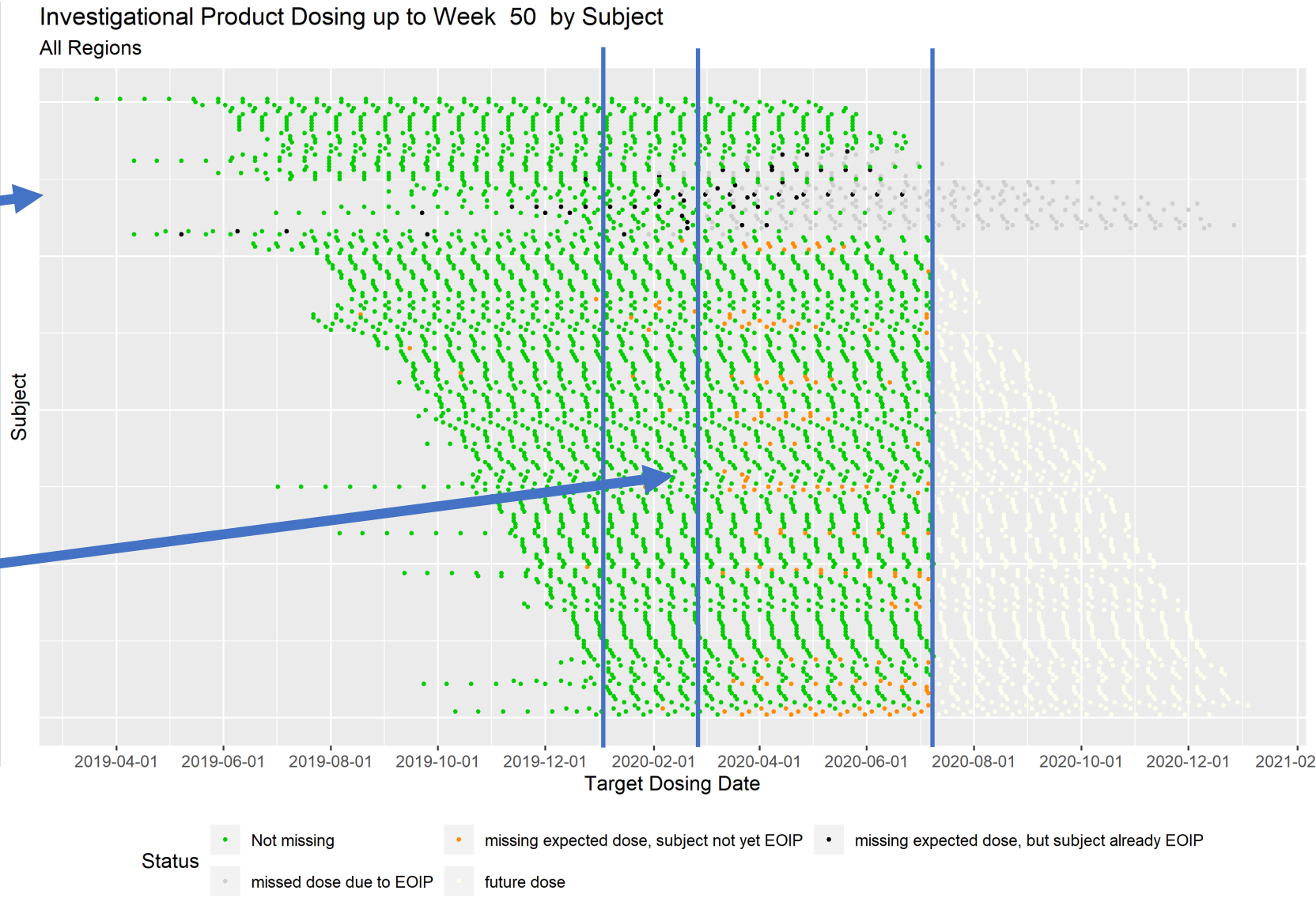
LOOKING ACROSS TIME SHEDS LIGHT ON COVID-19 IMPACT

Sorting Tip

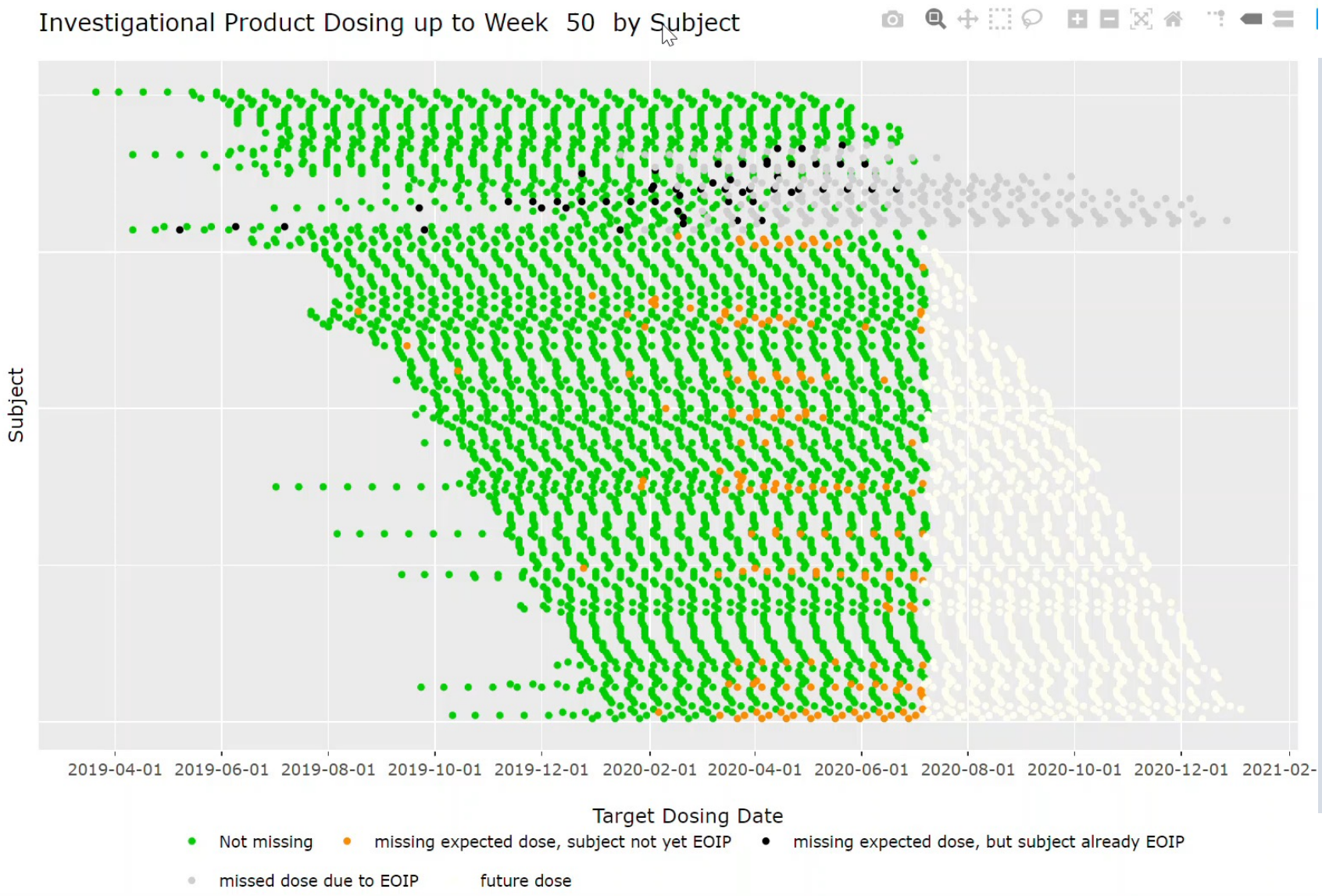
Order by EOIP status (EOIP subjects on top) followed by realization of doses (week 0 yes/no, week 2 yes/no… week 48 yes/no, week 50 yes/no)

Prior to 2020, subjects generally missed < 3 consecutive doses and then EOIP

From March 2020 -- consecutive missed doses, but still on study (not yet EOIP)



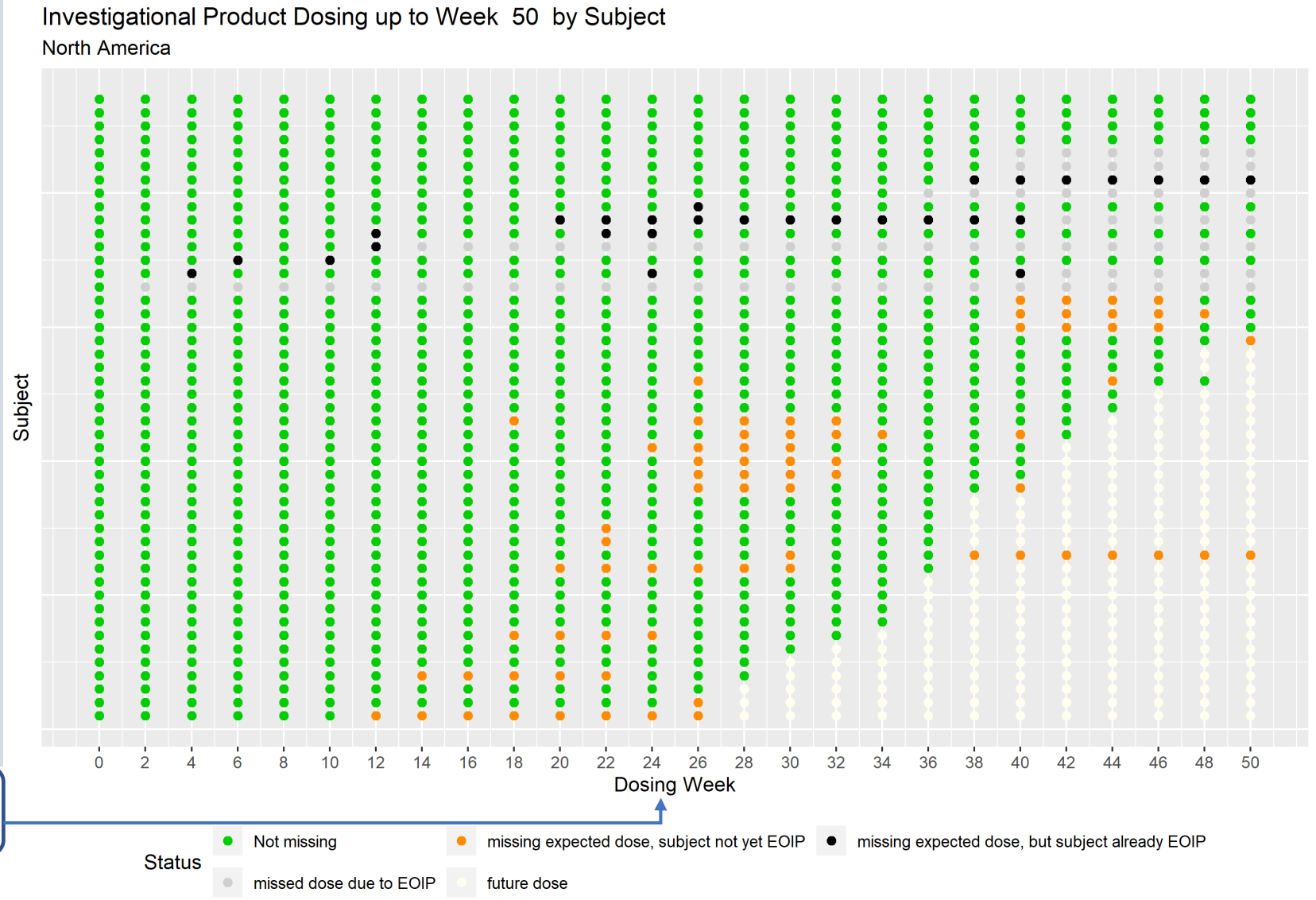
EXPLORING & ZOOMING IN: GGPLOTLY

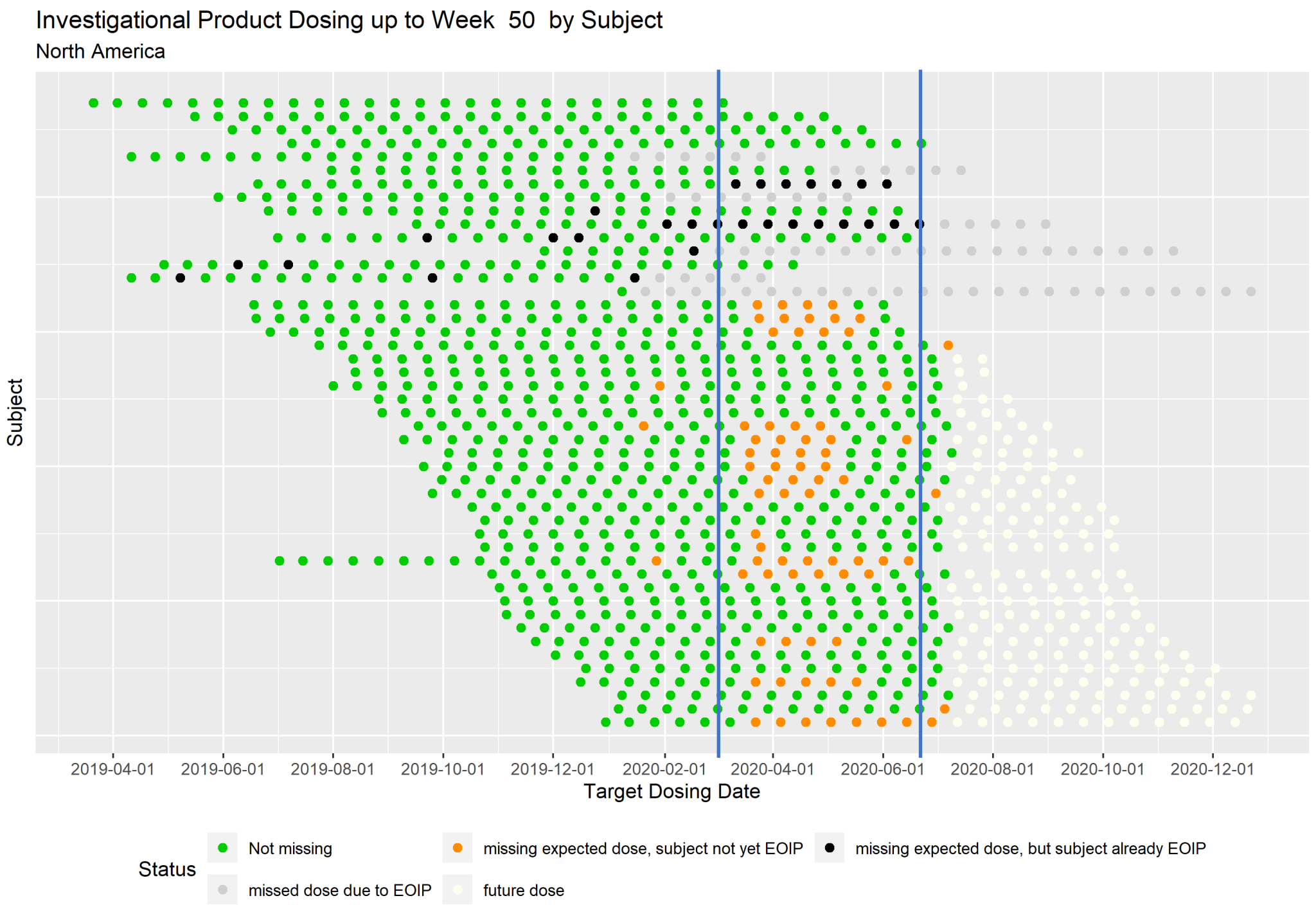


EXPLORING & ZOOMING IN: GGPLOTLY

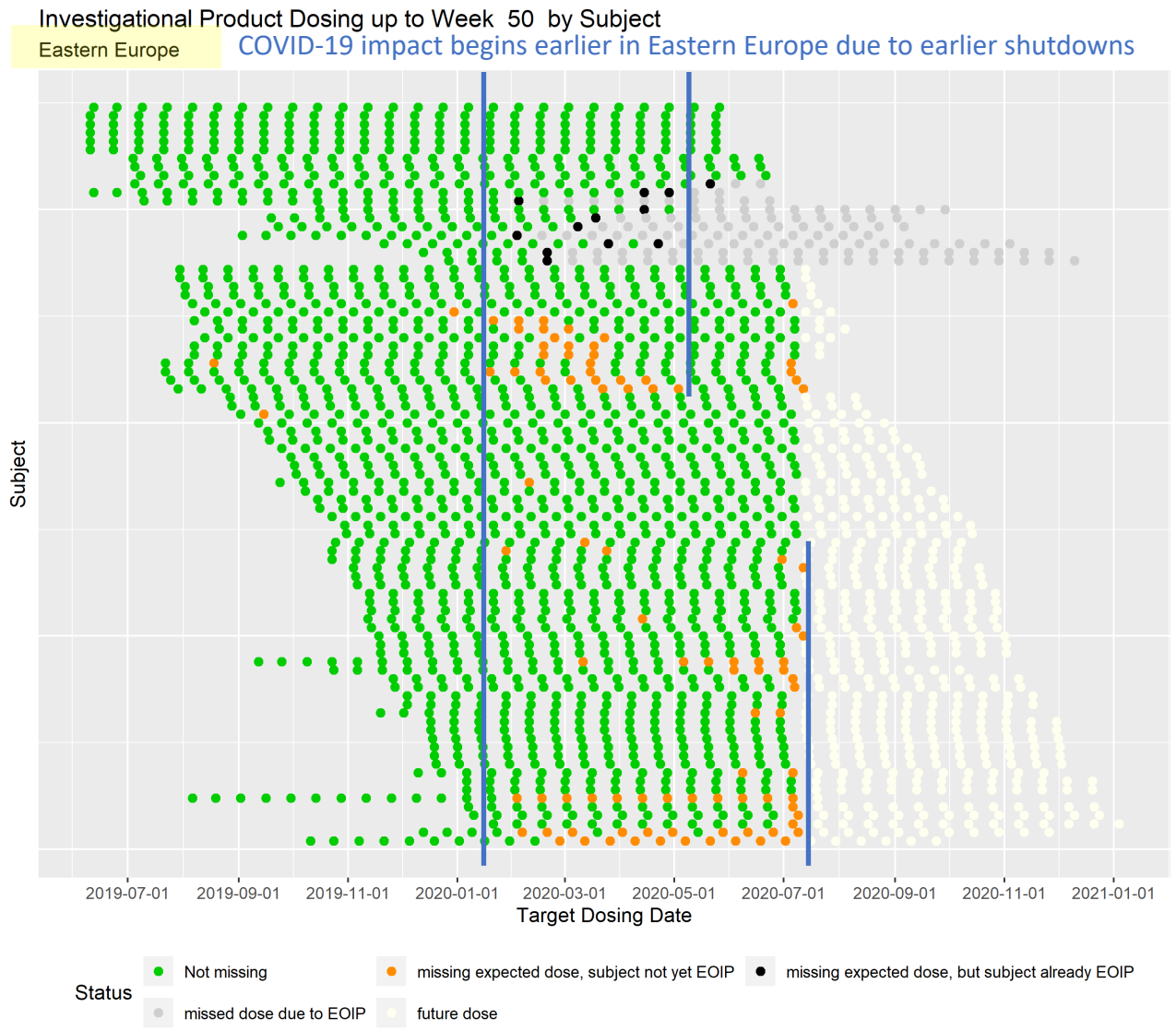
```
ggplotly(datasetname %>%

        mutate(doseweek = doseweek,
               targetipdate = as.Date(targetipdate),
               flag = factor(flag) ) %>%

        ggplot(aes(x=targetipdate, y=subject, group=doseweek,
        label=region)) +

        geom_point(aes(color=as.factor(flag))) %>%

plotly::layout(legend = list(x = 0.1, y = -0.1, orientation = 'h'))
```

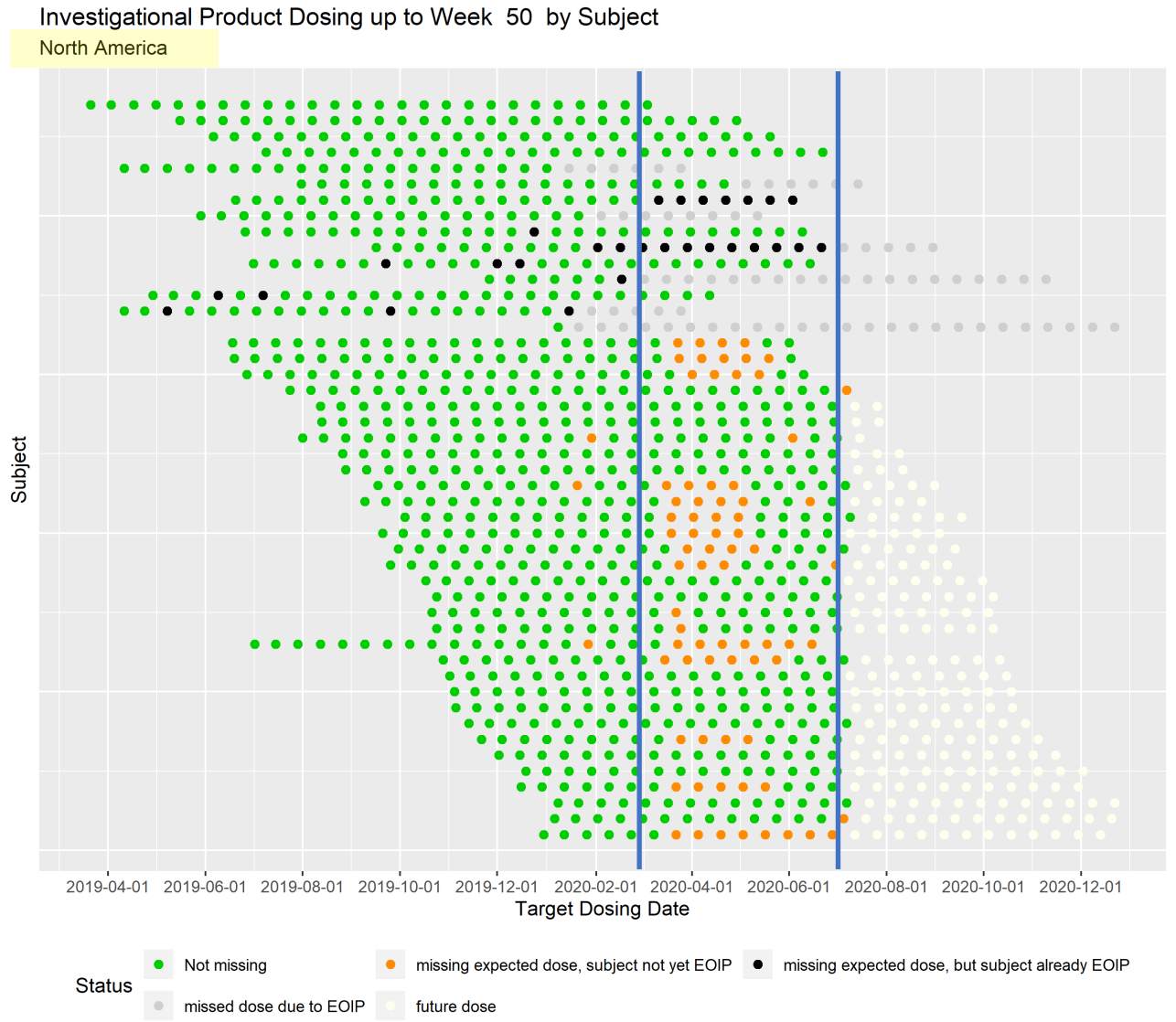
CLOSER LOOK: ZOOM IN & ASSESS IMPACTED DOSES



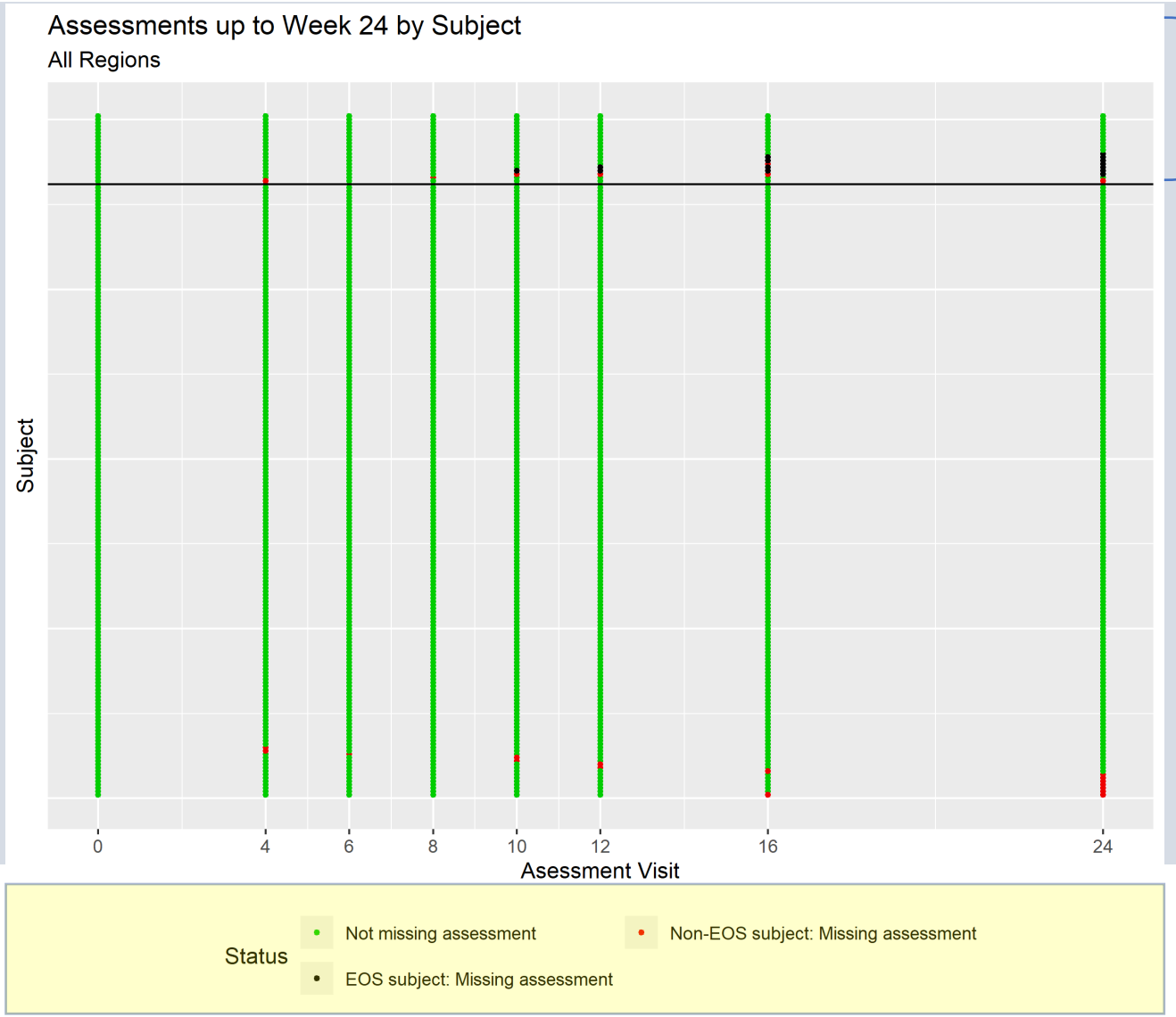

Investigational Product Dosing up to Week 50 by Subject
North America
Subject
2019-04-01
2019-06-01
2019-08-01
2019-10-01
2019-12-01
2020-02-01
2020-04-01
2020-06-01
2020-08-01
2020-10-01
2020-12-01
Target Dosing Date
Status
Not missing
missing expected dose, subject not yet EOIP
missing expected dose, but subject already EOIP
missed dose due to EOIP
future dose

DIFFERENT REGIONAL IMPACTS





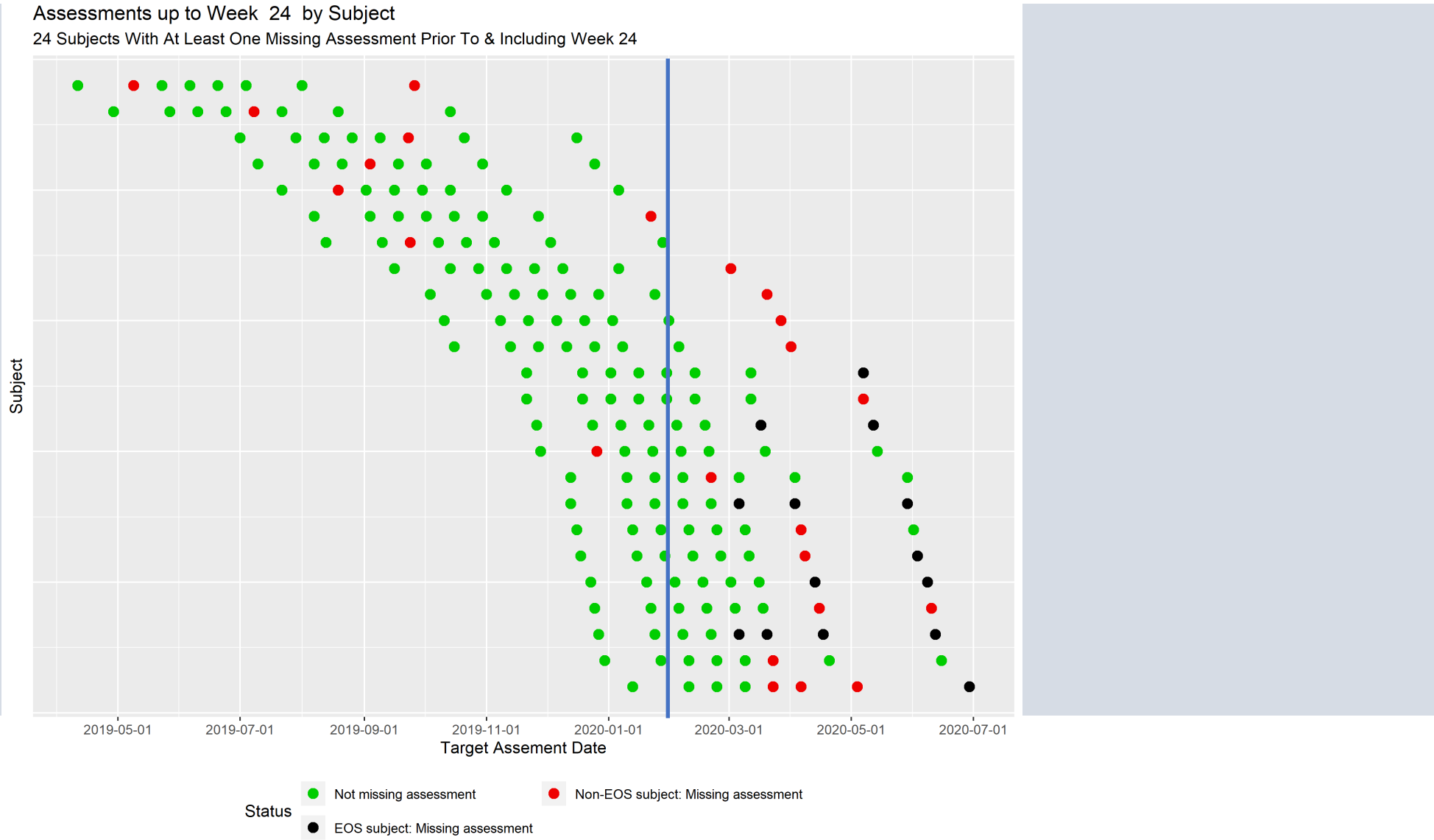
PRIMARY ANALYSIS: MISSING ASSESSMENTS UP TO WEEK 24



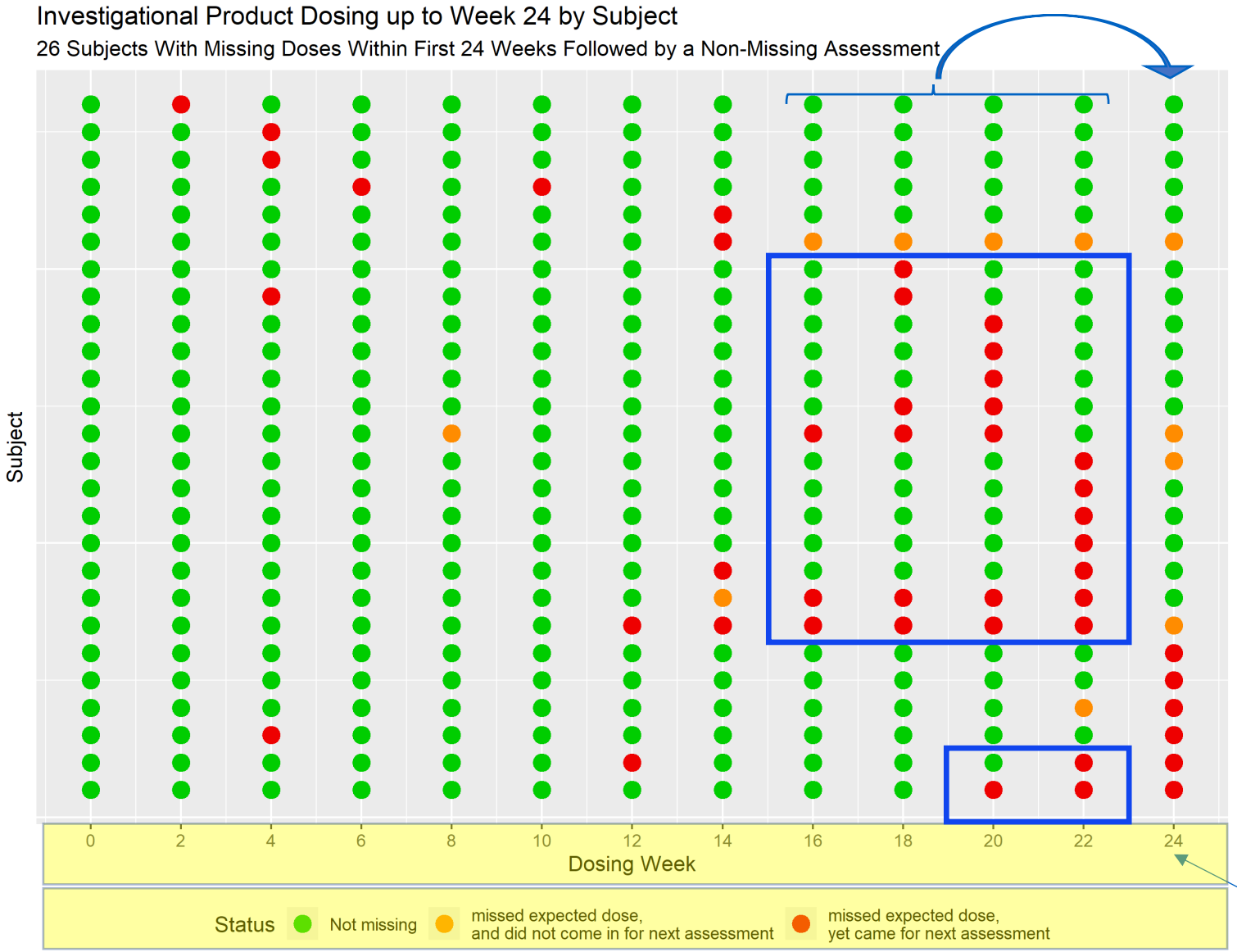
EOS

Relatively small proportion of missing assessments

ZOOMING IN: SUBJECTS WITH AT LEAST ONE MISSING ASSESSMENT



IP DOSING + ASSESSMENT PLOTS – HOW OFTEN DO SUBJECTS MISS IP DOSES, BUT STILL COME IN FOR ASSESSMENTS?



Sorting tip:
subjects who miss earlier doses on top, subjects who miss later doses on bottom

STATISTICAL CONSIDERATION:

if many subjects missed doses prior to primary endpoint assessment, consider sensitivity analysis

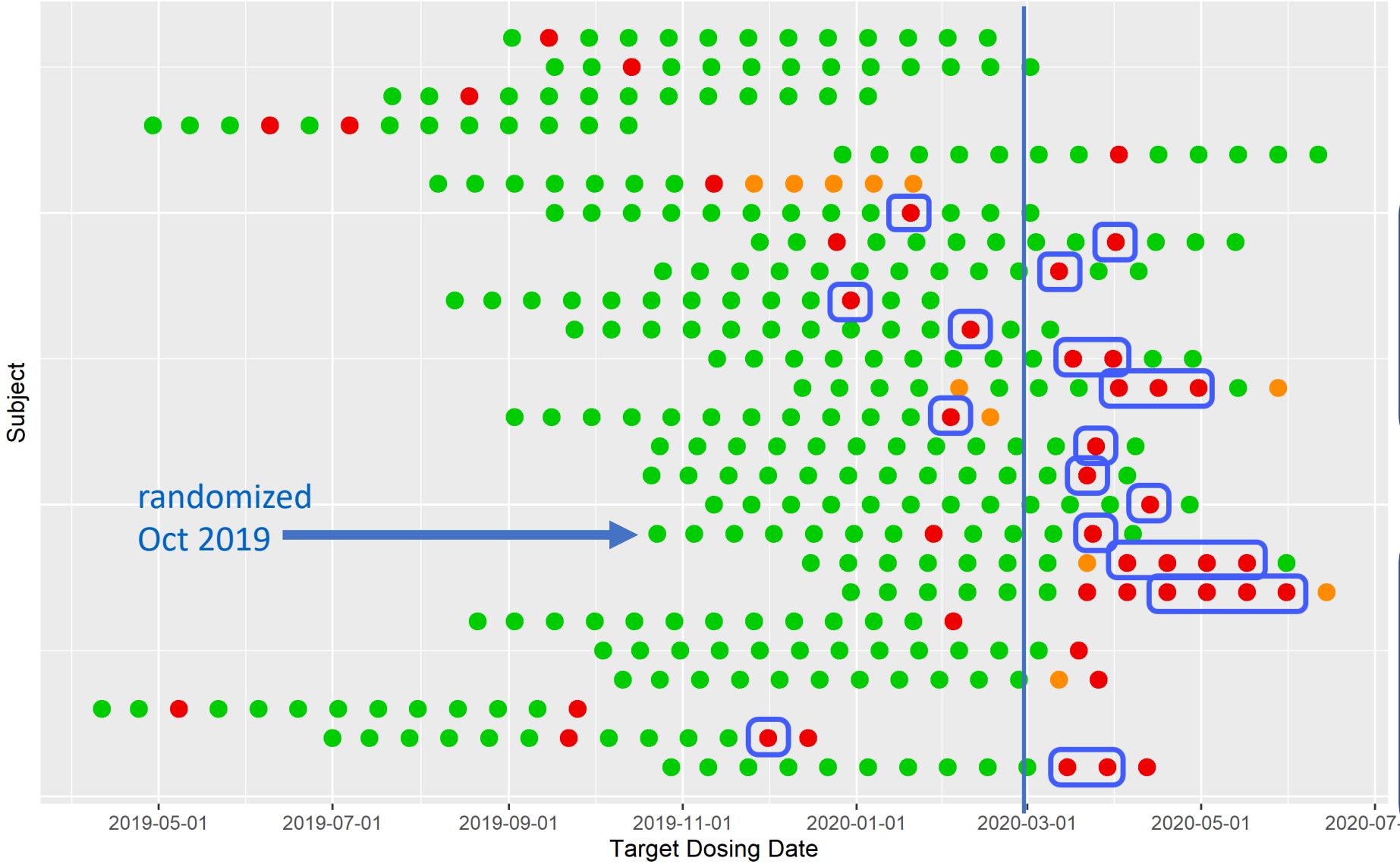
16 subjects miss critical doses

potentially diluted treatment effect at week 24

Primary Endpoint at Week 24

Investigational Product Dosing up to Week 24 by Subject

26 Subjects With Missing Doses Within First 24 Weeks Followed by a Non-Missing Assessment



16 subjects miss critical doses

potentially diluted treatment effect at week 24

Timing:

potential dilution begins in Q1 2020, and worsens in Q2 2020 – missingness attributable to COVID-19

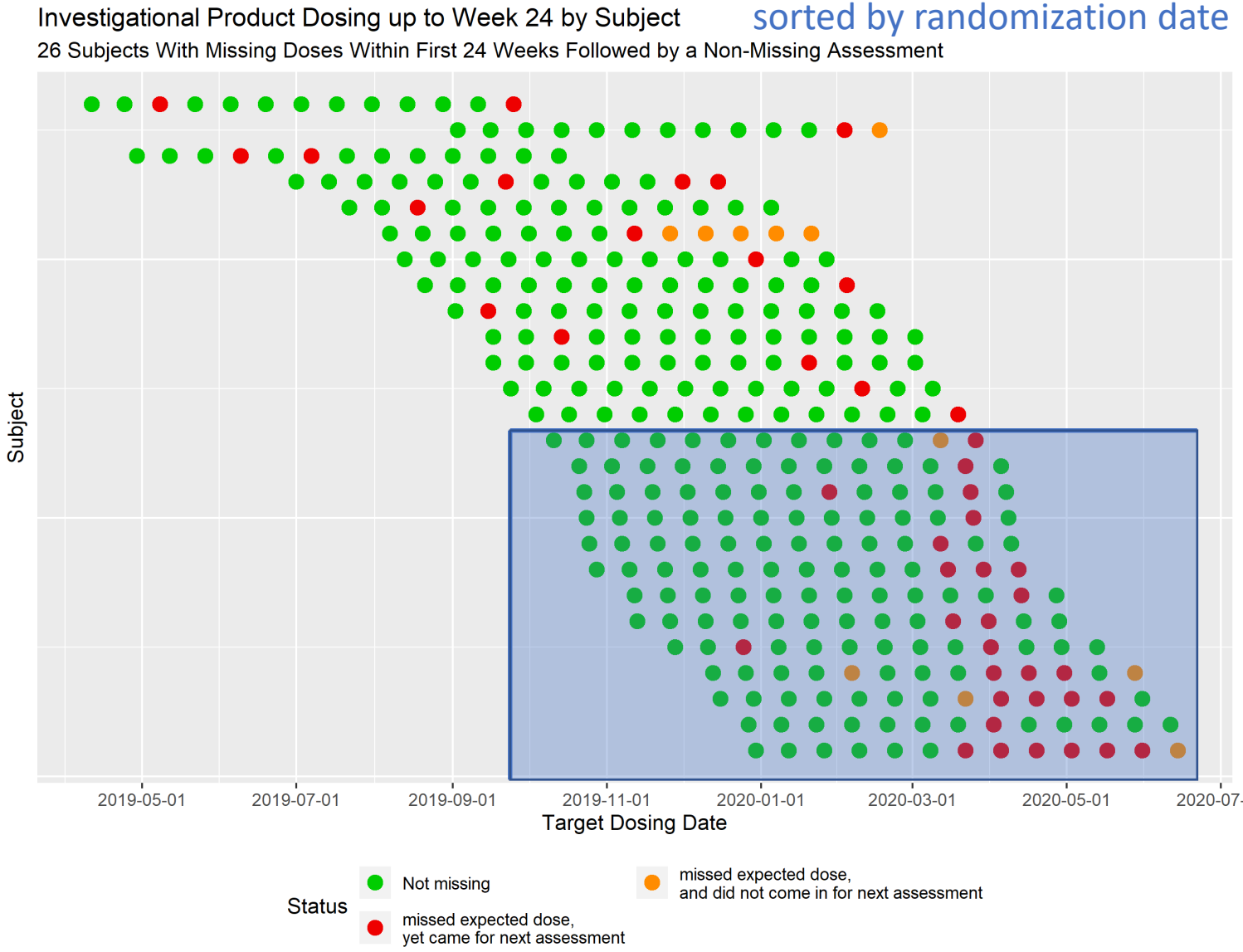
Mitigation:

Sensitivity analysis excluding subjects randomized after October 2019

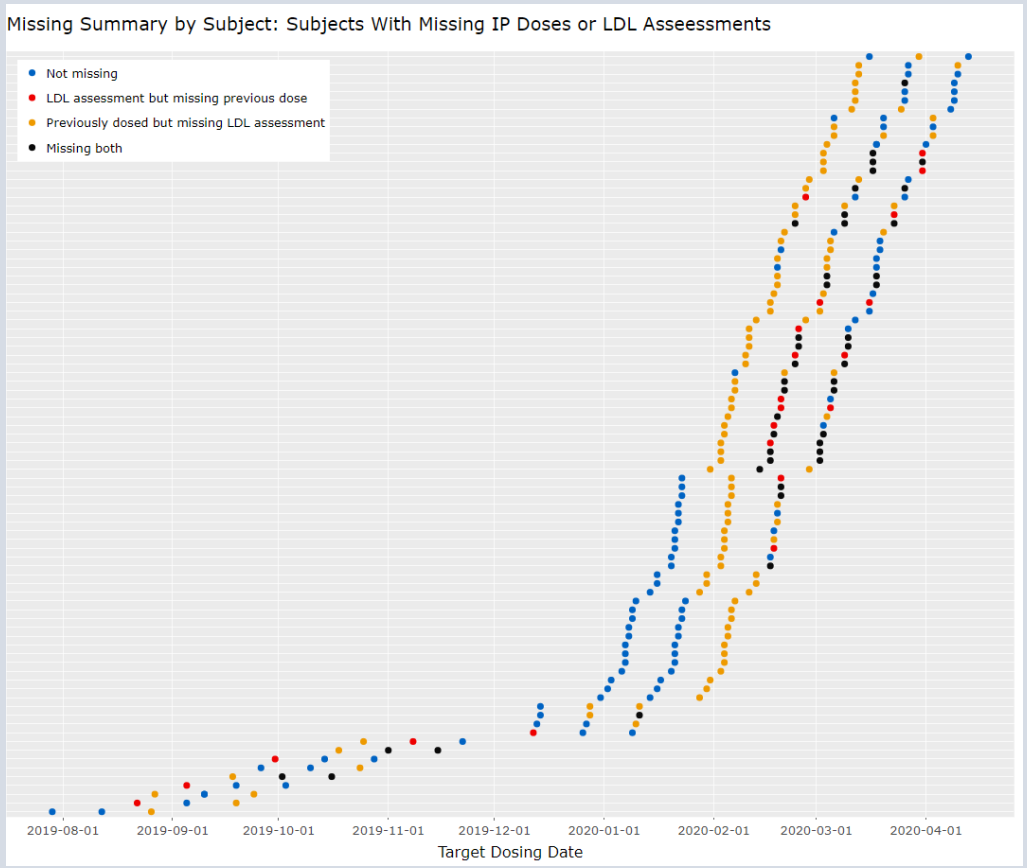
if power drops to an unacceptable level, consider increasing sample size

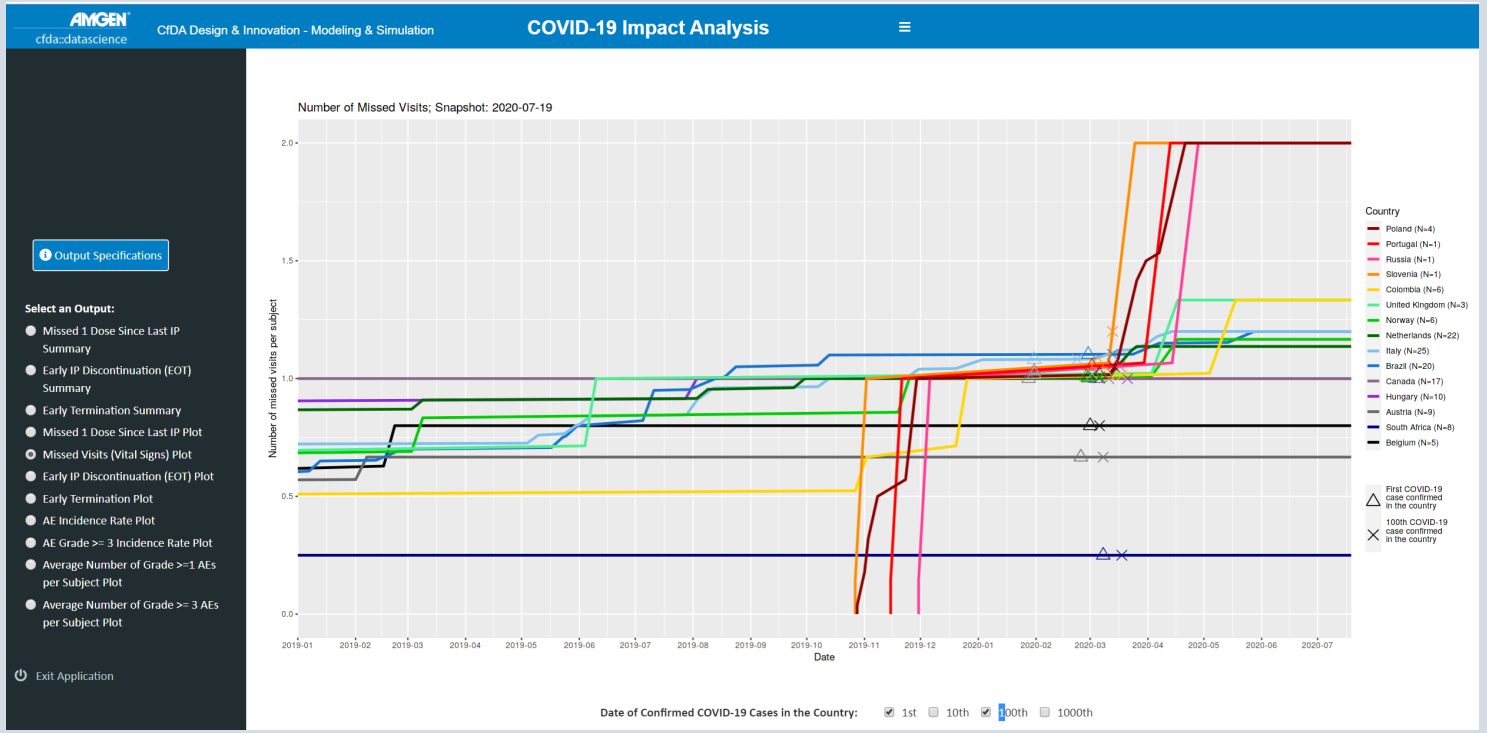
IDENTIFYING EXCLUSION OF SUBJECTS FOR MODIFIED FAS

- March is time we begin seeing COVID-19 impact.
- Earliest randomization date of subject missing critical doses yet coming in for assessments is October 2019
- To avoid bias, exclude subjects indiscriminately by randomization date (no post-baseline info used)
- Evaluate power loss when using modified FAS



EXTENSIONS & OTHER COVID-19 IMPACT ANALYSES BY AMGEN DESIGN & INNOVATION GROUP





Available for all active Amgen studies and updated daily using RAVE data

CONSIDERATIONS AFTER EVALUATING PLOTS

Keep original sensitivity analyses

Further Mitigation: add a modified FAS for supportive analysis

- Full Analysis Set – all randomized subjects
- **Modified Full Analysis Set** – all subjects who were randomized *prior to* the earliest randomization date of subjects who missed critical doses attributable to the COVID-19 2020 outbreak resulting in a potentially diluted treatment effect.
- Keep NRI approach of binary endpoint at Week 24 –
  mFAS reduces power (still > 80%), but would provide an **unbiased** and **undiluted** estimate for the treatment effect for all endpoints

SUMMARY OF SELECT MITIGATION STRATEGIES

Missed both dose & assessment
(e.g. pts not going to clinic)

Focus is on proportion of missing visits.
How are primary and secondary endpoints impacted?

Proportion of missingness is:
- small relative to overall data points
  → less concerning
- attributed to COVID-19 and is balanced between treatment groups
  → **MAR** assumption

Proportion of missingness is:
- large relative to overall data points
  → effect on efficiency could be concerning
- large even before COVID-19, imbalanced between treatment groups and/or baseline characteristics
  → **MNAR** assumption (consider control-based pattern multiple imputation)

Use sensitivity analyses to check robustness

ACKNOWLEDGEMENTS

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