J.P. Morgan Healthcare Conference

January 13, 2020

Peter Hecht, CEO

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Priorities for 2020

sGC

1

DN praliciguat partnering:

out-license discussions based on promising phase 2

2

SCD olinciguat phase 2 completion:

potential for raising standard of care across four therapeutic domains

3

CNS IW-6463 advancement:

advancement from successful phase 1 in healthy volunteers to ongoing study in elderly subjects

1 Praliciguat in diabetic nephropathy (DN): out-license discussions based on promising phase 2

Data support further development → **Out-license discussions underway**

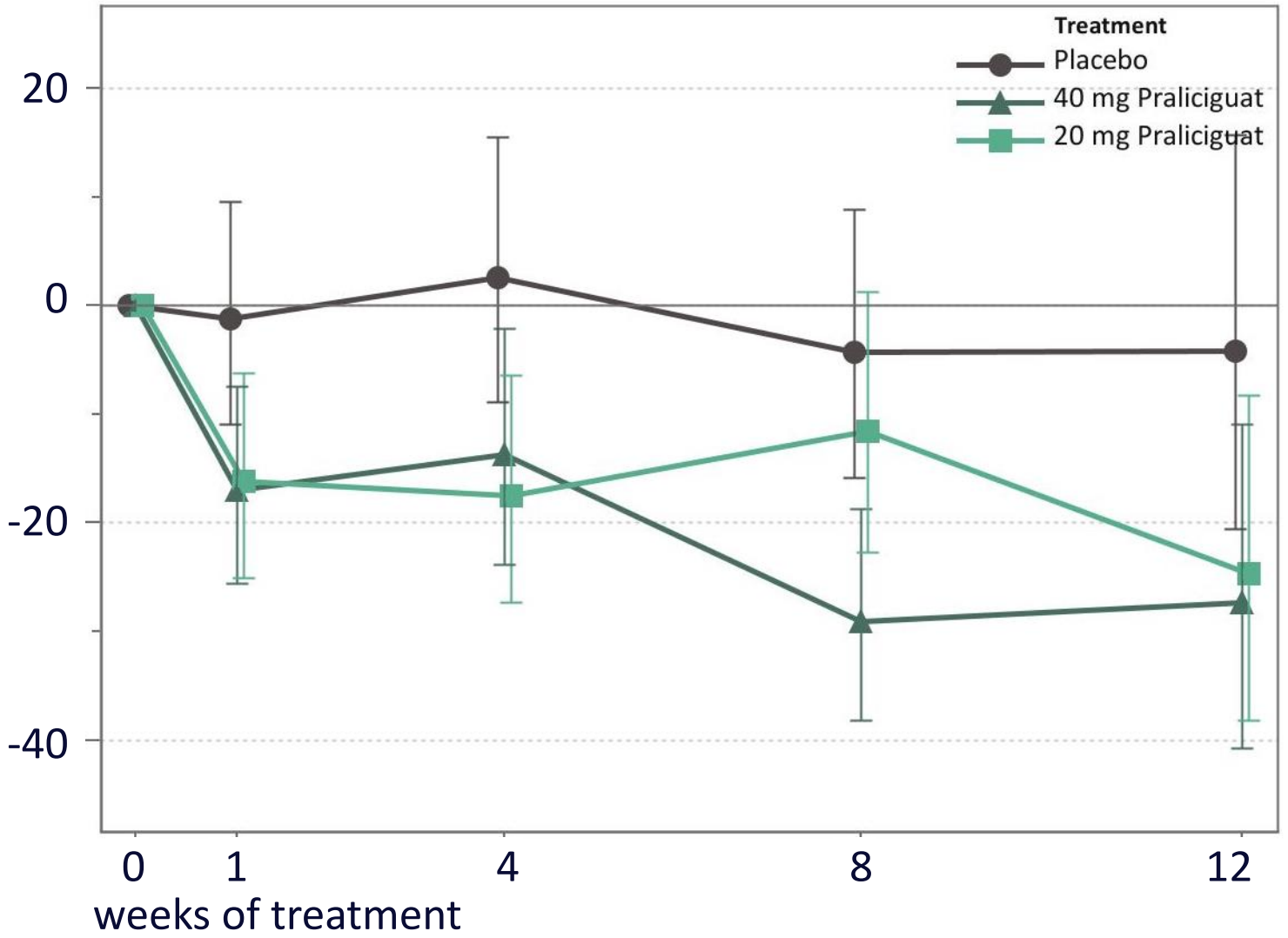
- UACR reductions on top of standard of care
  - 20%[1] placebo-adjusted (p=0.0303[2])
  - 24%[1] absolute change from baseline
- reductions in blood pressure, HbA1c, total and LDL cholesterol
- favorable safety profile, consistent with previous studies
- attractive dosing and PK relative to others in class

1. Modified intent-to-treat population, pooled praliciguat 20 and 40mg dose, placebo-adjusted average of weeks 8 and 12 (primary endpoint)
2. Nominal p-value; not adjusted for multiplicity

Phase 2 showed promising improvement in UACR

% UACR change from baseline

LS mean (90% CI) change UACR in (mg/g) (mITT)[1]



(90 % CIs by dose & timepoint)

1. mITT: modified intent-to-treat population n=133 excludes data from site 00A where data inconsistencies were observed in both the treatment and control groups

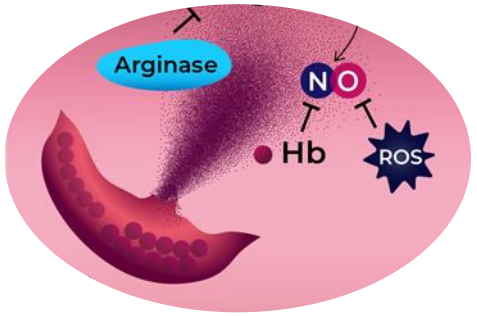
2 Olinciguat in sickle cell disease (SCD): potential for raising standard of care across four therapeutic domains

Dynamic mechanism - alone or complementing approved treatments → **Topline phase 2 results mid-2020**

- upstream + downstream pharmacological intervention
- impact potential in four clinical domains: anemia, daily symptoms, VOC, and organ protection--not fully addressed by approved therapies
- oral, QD drug for use in a broad range of SCD patients
- STRONG SCD trial designed to assess safety and pharmacodynamic effects across full dose range

Olinciguat: upstream and downstream intervention in SCD

Increased hemolysis leads to reduced nitric oxide state



sGC restores deficient nitric oxide signaling

Upstream

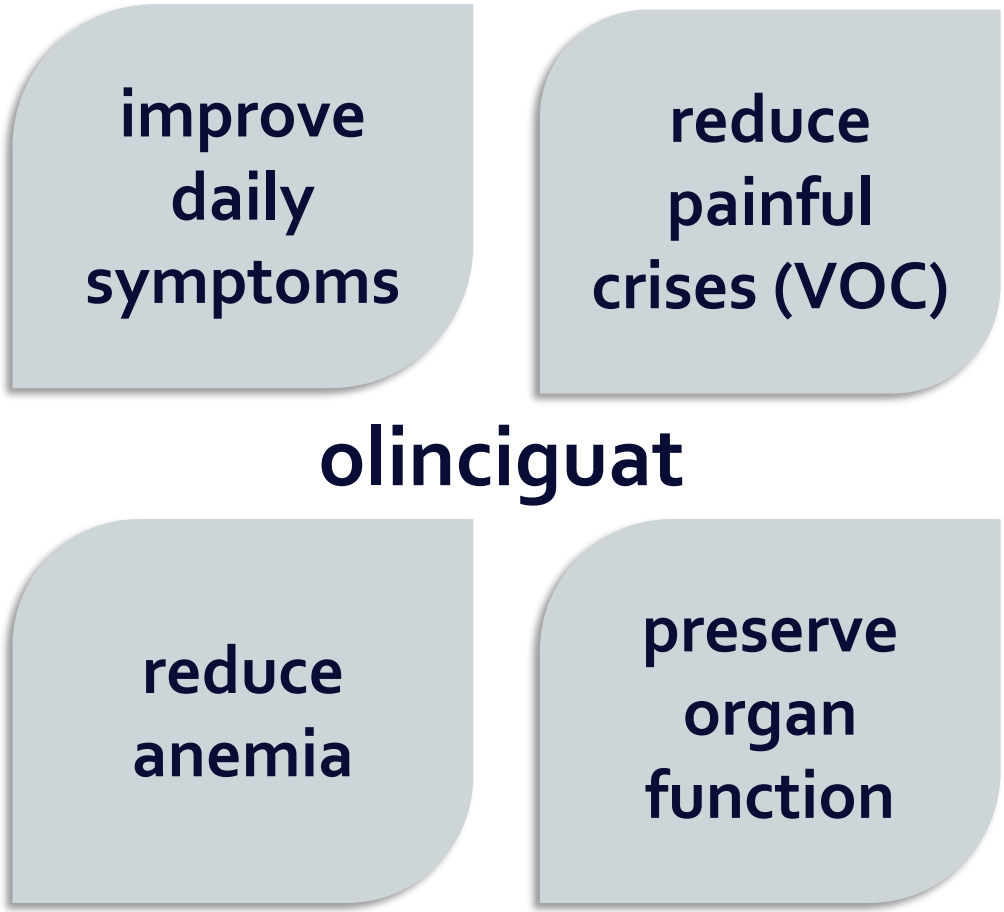
- increased HbF leads to reduced proportion of sickled RBCs1

Downstream

- improved blood flow
- decreased vascular inflammation & cell adhesion
- improved endothelial integrity

1. Conran, N., & Torres, L. (2019). cGMP modulation therapeutics for sickle cell disease. *Experimental Biology and Medicine*, 244(2), 132–146.

Potential to raise standard of care across four therapeutic domains



- newly approved therapies each target a single clinical domain…
- …olinciguat has the potential to improve four
- daily symptoms and end-organ protection remain unaddressed, decreasing QoL and increasing mortality
- further improvement in anemia and/or VOC possible with olinciguat alone or as add-on therapy serving broad SCD patient population

STRONG SCD

Olinciguat phase 2 trial designed to support rapid advancement

Topline results expected mid-2020

DESIGN

- double blind
- global sites
- 4 dose levels
- up to 88 patients aged 16 – 70
- 12-week treatment in all SCD genotypes

OBJECTIVES

- assess safety and tolerability
- confirm PK profile in SCD patients
- development of the CYCN fit-for-purpose patient-reported outcomes (ePRO) instrument
- signs of pharmacodynamic effect: biomarkers (Hb, HbF, inflammation, adhesion) and daily symptom effects

INSIGHTS FOR PHASE 3 DESIGN

- endpoint selection based on results (biomarkers and ePRO)
- determine study sample size and dose(s)

3 IW-6463 in CNS: advancing development for treatment of serious neurodegenerative diseases

Ph 1 showed safety, target engagement, CNS exposure

Additional clinical studies in 2020 to accelerate and de-risk program

Preclinical evidence: stimulation of nitric oxide-cGMP pathway improves determinants of brain health

Impaired brain function associated with low nitric oxide-cGMP

Enhanced NO-cGMP in the CNS leads to:

- enhanced neuronal function
- increased cerebral vascular function
- decreased microglial activity
- improved mitochondrial output

Potential for improved brain health

1. Cyclerion's pre-clinical work www.cyclerion.com

IW-6463 potential to restore nitric oxide-cGMP signaling

Nitric oxide insufficiency leads to

- neuroinflammation and neurodegeneration
- impaired neurovascular blood flow

Improved brain health

- decreased inflammation
- increase blood flow
- neuroprotection and enhanced cognition

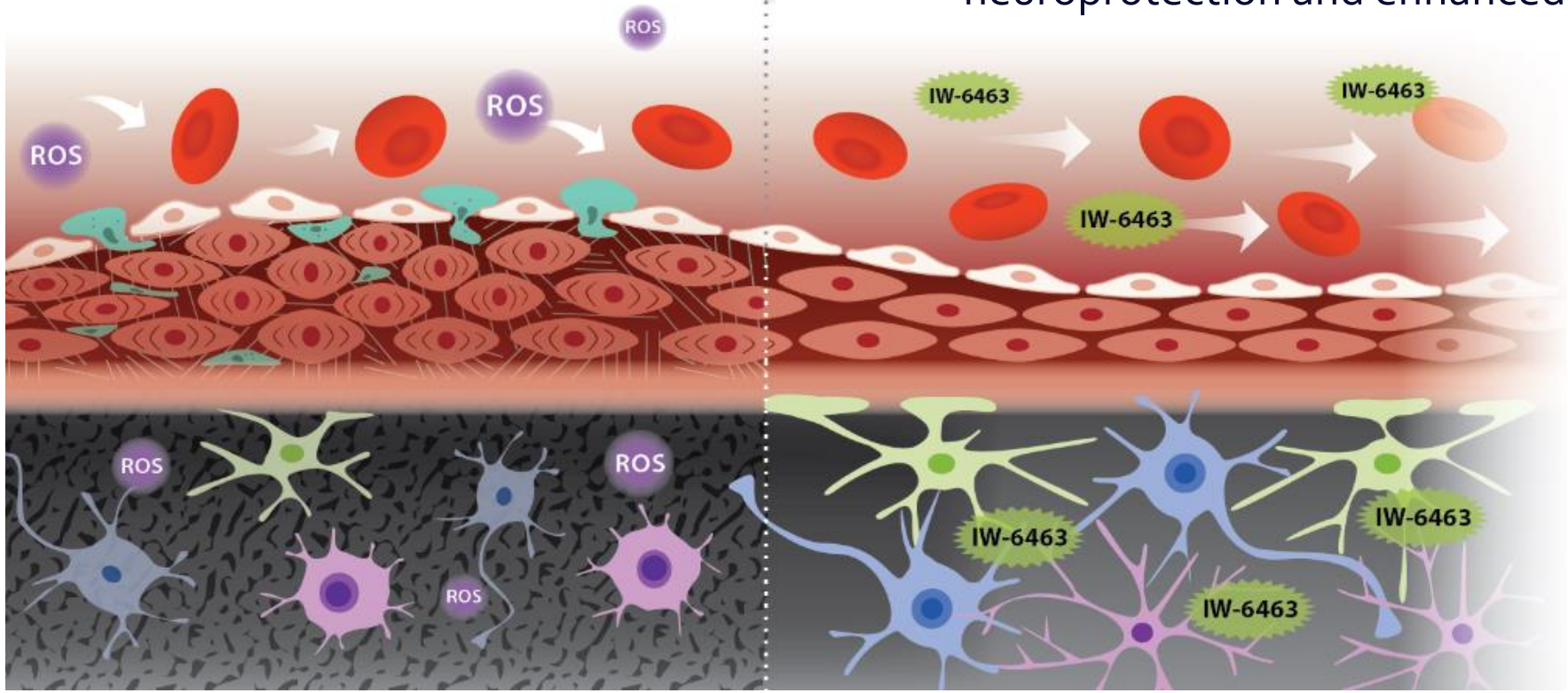


Figure adapted from Tobin, Zimmer et al. J Pharmacol Exp Ther 2018;365:664-675. Copyright © 2018 The Author(s).

Positive phase 1 IW-6463 results support further development

Newly released—completed December 2019

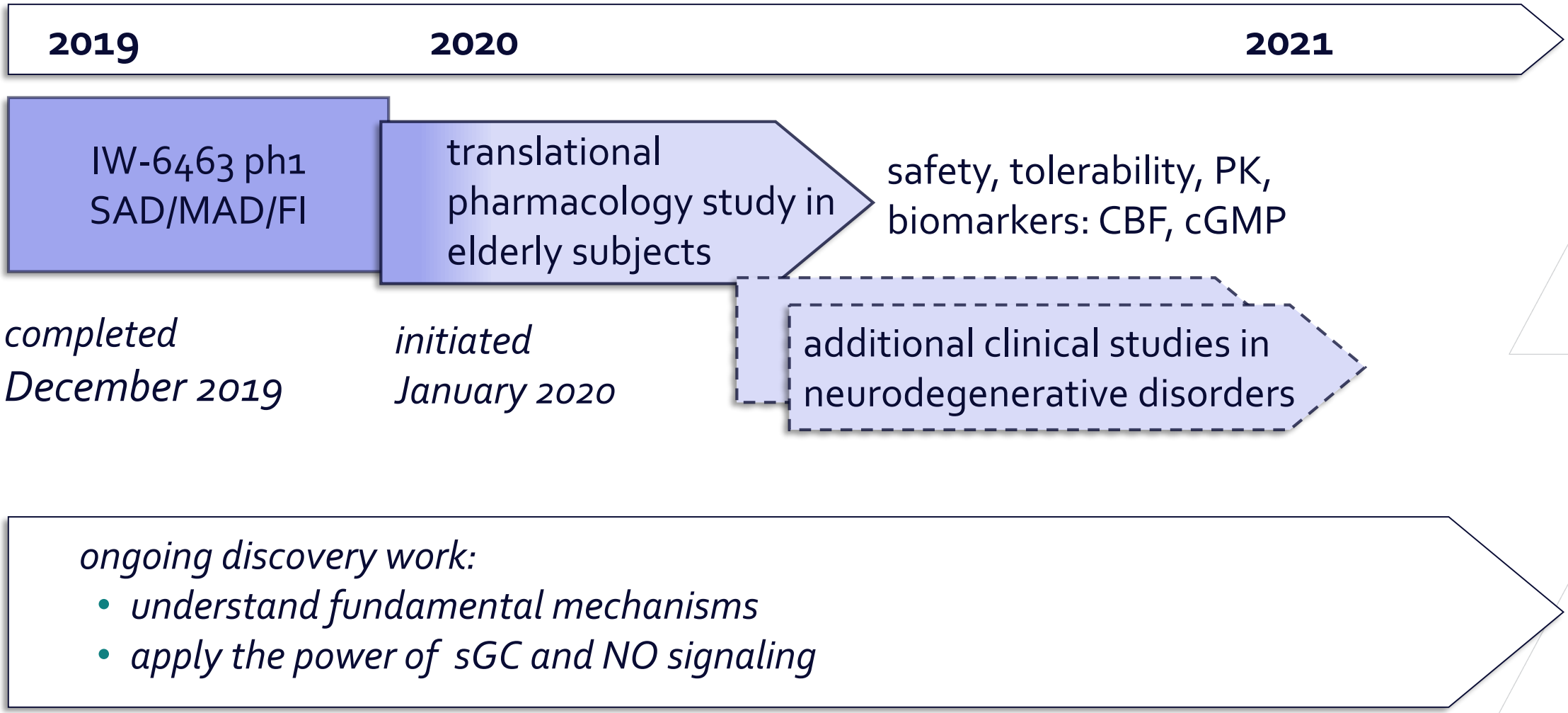
Phase 1 study design

- 3 stage: SAD, MAD and food interaction
- 110 healthy volunteers
- age range 18-63
- assessed safety, PK (blood & CSF)
- wide dose / exposure range tested

Insights

- CNS drug presence at levels expected to be pharmacologically active
- QD dosing, linear and predictable PK
- may be taken with or without food
- evidence of target engagement (blood pressure)
- well-tolerated at all dose levels
- all AEs mild in severity, no SAEs

Clinical direction: accelerate and de-risk into high value CNS indications



Cyclerion

2020 catalysts across programs

- partnering
- clinical trials

~$102M cash[1] and reduced burn support our priorities into Q2 2021

Team, talent and intensity to deliver

1. Preliminary, unaudited unrestricted cash, cash equivalents and restricted cash balance as of Dec 31, 2019

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