



 agios | **AGIOS**
October 2020



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This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Agios' plans, strategies and expectations for its and its collaborator's preclinical, clinical and commercial advancement of its drug development programs including TIBSOVO® (ivosidenib), IDHIFA® (enasidenib), mitapivat, vorasidenib, AG-270, and AG-946; the potential benefits of Agios' product candidates; its key milestones and guidance for 2020; its strategic vision and goals for 2025; its plans regarding future data presentations; its financial guidance regarding the period in which it will have capital available to fund its operations; and the potential benefits of its strategic plans and focus. The words "anticipate," "expect," "goal," "hope," "milestone," "opportunity," "plan," "potential," "possible," "strategy," "will," "vision," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios or its collaborators is developing will successfully commence or complete necessary preclinical and clinical development phases, or that development of any of Agios' product candidates will successfully continue. There can be no guarantee that any positive developments in Agios' business will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this presentation and various remarks we make during this presentation could also be affected by risks and uncertainties relating to a number of other important factors, including, without limitation: risks and uncertainties related to the impact of the COVID-19 pandemic to Agios' business, operations, strategy, goals and anticipated milestones, including its ongoing and planned research activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; Agios' results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. FDA, the EMA or other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Agios' ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures; competitive factors; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to maintain key collaborations; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' public filings with the SEC. Any forward-looking statements contained in this presentation and various remarks we make during this presentation speak only as of the date hereof, and Agios expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.



We are
driven by our
sense of
urgency to
help patients.



“On a bad day, it’s like watching some electronic toy slowly lose the battery.”
—Tamara S., Minnesota



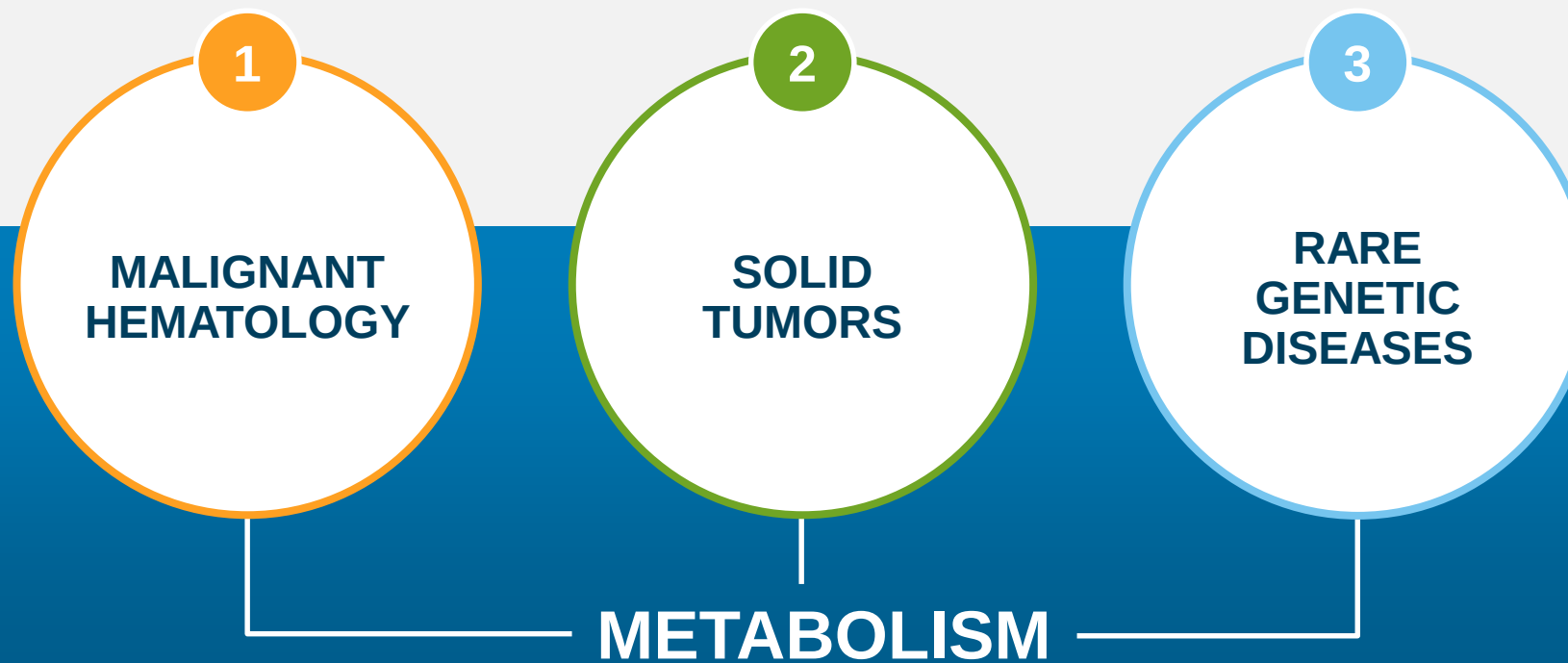
“The disease has affected my career. I spent 11 years to get a PhD in nutrition...My heart wants more but my body can’t handle it.”

—Tamara S., Minnesota

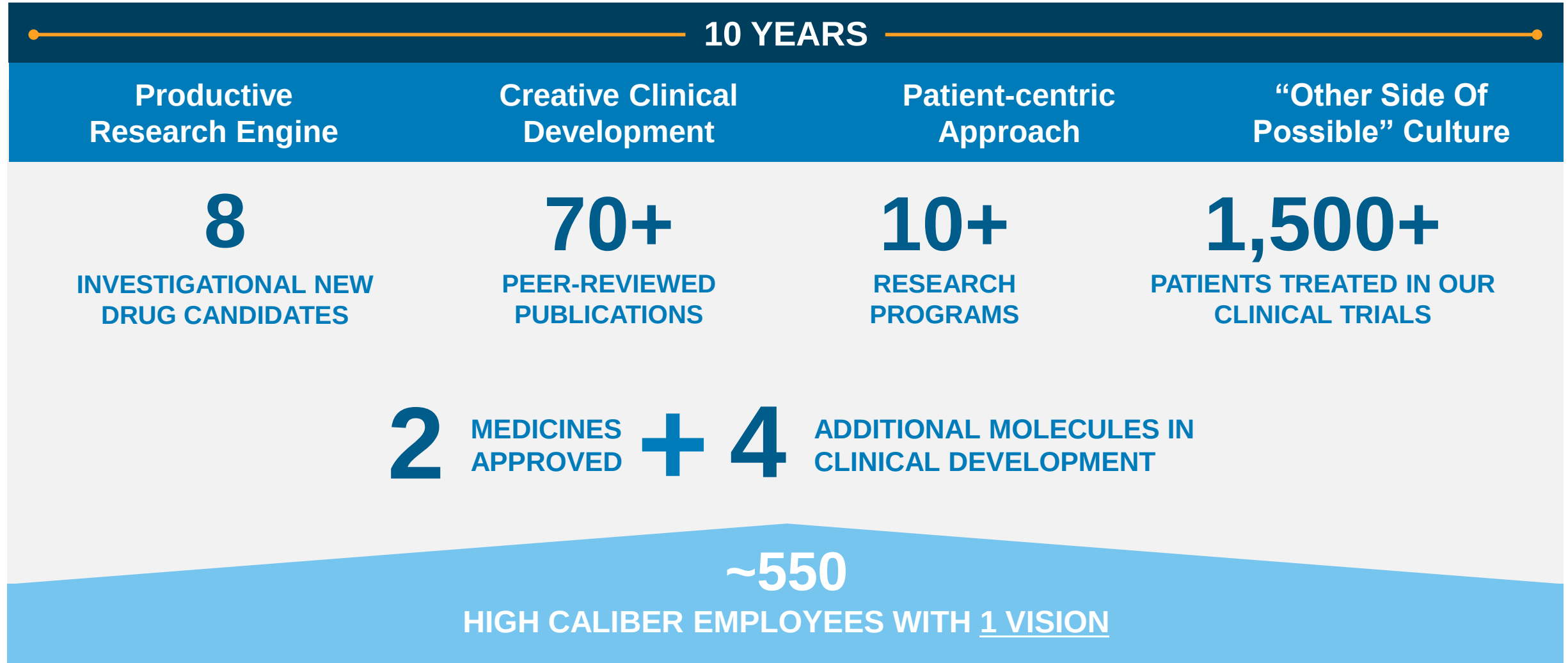
Currently 50 years old. Diagnosed with PK deficiency at the age of 6.

Our Strategy is Clear

For more than a decade, our mission has been to create **differentiated, small molecule medicines for patients** in three focus areas – malignant hematology, solid tumors and rare genetic diseases – based on our unique expertise in **cellular metabolism** and adjacent areas of biology



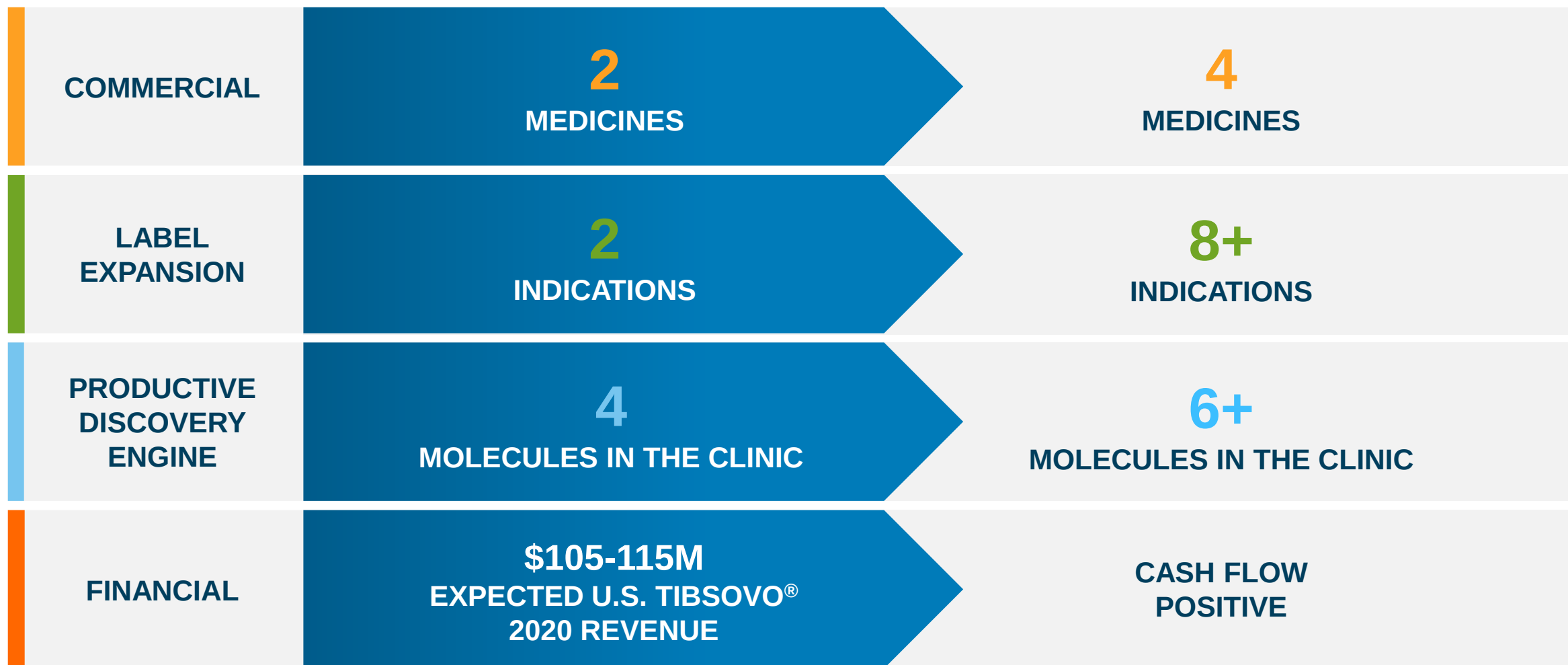
Our People and Culture Fuel Incredible Productivity, Strategic Focus and Continuity from Early Research to Market



Agios 2025 Vision: Focused Innovation. Ambitious Development. Transformative Treatments for Patients Across Three Focus Areas.

NOW

2025



Anticipated Upcoming Milestones

RARE GENETIC DISEASES

- Mitapivat ACTIVATE and ACTIVATE-T topline data in PK deficiency between YE 2020 and mid-2021
- Finalize pivotal development plan for mitapivat in thalassemia by the end of 2020; initiate a pivotal program in 2021
- Finalize pivotal development plan for mitapivat in sickle cell disease and initiate pivotal program in 2021

MALIGNANT HEME

- Achieve full-year U.S. revenue for TIBSOVO® \$105-115M
- EU regulatory process for TIBSOVO® in R/R AML ongoing with a CHMP opinion expected by YE 2020

SOLID TUMORS

- Mature OS data from ClarIDHy study of TIBSOVO® in the third quarter 2020; cholangio sNDA filing in the first quarter 2021





CREATING MEDICINES IN
THREE FOCUS AREAS

1

Malignant Hematology

2

Solid Tumors

3

Rare Genetic Diseases



CREATING MEDICINES IN
THREE FOCUS AREAS

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Rare Genetic Diseases

Significant Growth Potential in Malignant Hematology

~4K

**PATIENTS IN
U.S. & EU**

**IDH1 Mutant Acute Myeloid
Leukemia (AML)**

TIBSOVO®

R/R AML	U.S. Approval; MAA Under Review
1L Monotherapy	U.S. Approval
1L HMA Combo	Phase 3
1L 7+3 Combo	Phase 3

<1K

**PATIENTS IN
U.S.**

**IDH1 Mutant Myelodysplastic
Syndrome (MDS)**

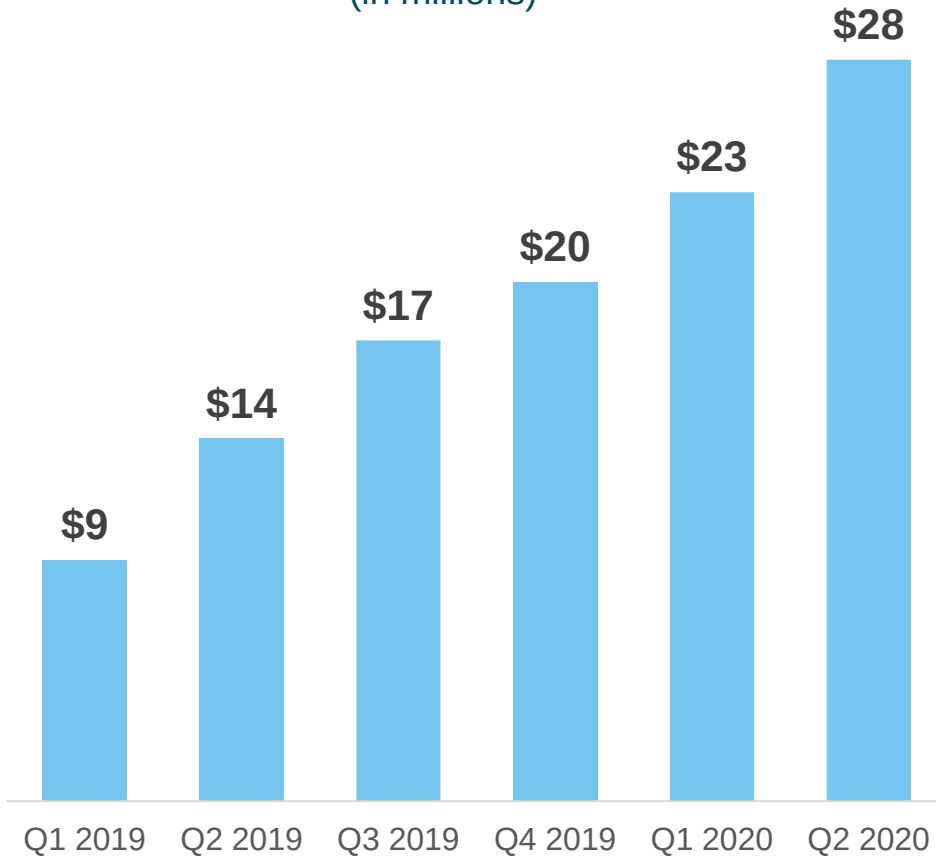
TIBSOVO®

R/R MDS	Phase 1 Expansion
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Q2 Growth Driven by Increased Demand in Both R/R and Frontline AML Segments and Expanding Customer Base

TIBSOVO® Revenue
(in millions)



22% Growth

In Product Revenue Quarter-over-Quarter



\$105 – 115M

U.S. Net Sales Guidance for 2020



15% Increase

In Unique Prescribers Quarter-over-Quarter



~1,600

Patients Treated Since Launch

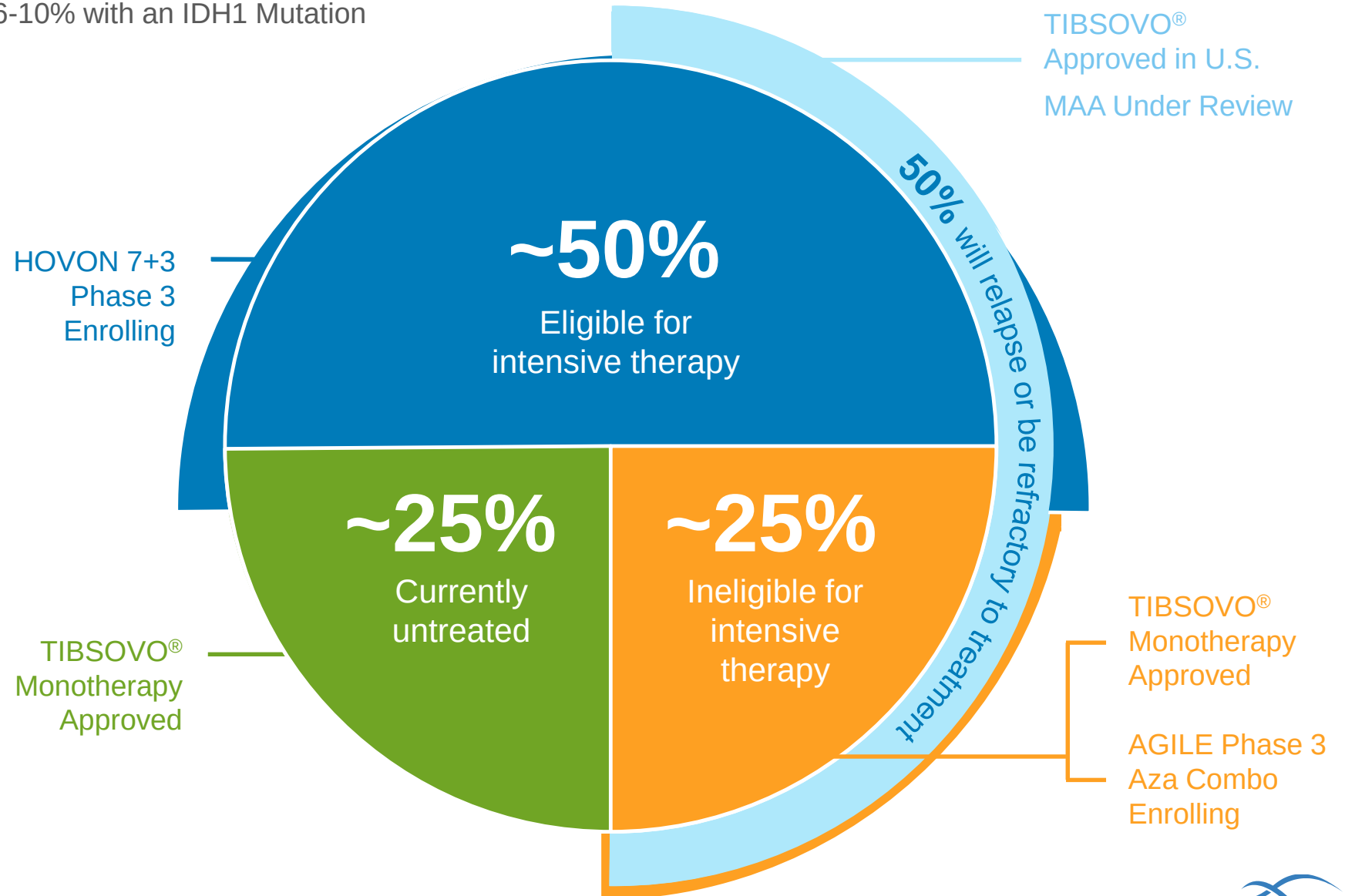
Source: Agios estimates



50K AML Patients Diagnosed Per Year in U.S. and EU

6-10% with an IDH1 Mutation

Advancing
Toward Largest
Opportunity for
mIDH1 AML:
Intensive and
Non-Intensive
Therapy
Combinations



Sources: SEER. Cancer Stat Facts: AML 2015 and Epiphany EPIC oncology numbers; American Cancer Society. AML 2017.





CREATING MEDICINES IN
THREE FOCUS AREAS

1

Malignant Hematology

2

Solid Tumors

3

Rare Genetic Diseases

Four Distinct Solid Tumor Opportunities Across Three Clinical Molecules

~2-3K

**PATIENTS IN
U.S. & EU**

**IDH1 Mutant
Cholangiocarcinoma**

TIBSOVO®

R/R Cholangio

sNDA expected
in Q1 2021

~9K

**PATIENTS IN
U.S. & EU**

**IDH Mutant
Low Grade Glioma**

Vorasidenib

Low-grade Glioma

Phase 3

~9K

**PATIENTS
IN U.S.**

**MTAP-Deleted Non-
Small Cell Lung Cancer**

AG-270

2nd Line NSCLC

Phase 1
Combo

~10K

**PATIENTS
IN U.S.**

**MTAP-Deleted
Pancreatic Cancer**

AG-270

**1st or 2nd Line
Pancreatic Cancer**

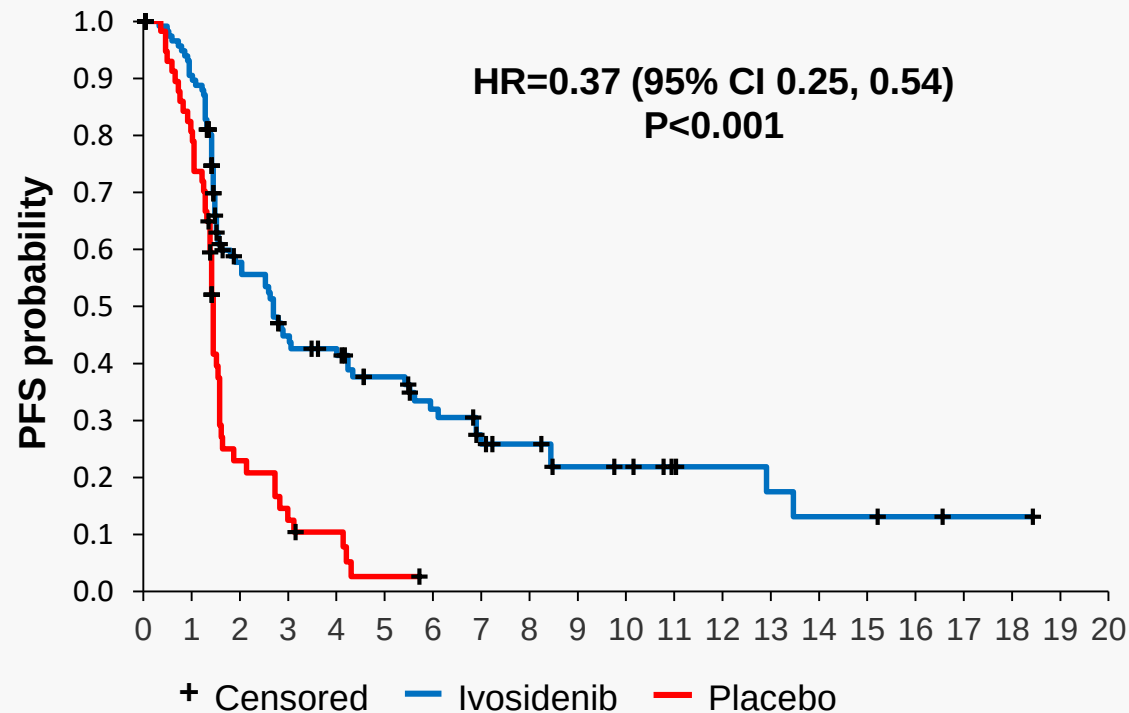
Phase 1
Combo



Established Utility of IDH Inhibition in Solid Tumors with Positive ClarIDHy Phase 3 Study of TIBSOVO® in Second-line or Later Cholangiocarcinoma

Mature OS from ClarIDHy Phase 3 expected Q3 2020; sNDA planned for Q1 2021

Phase 3 ClarIDHy Study Achieved Primary Endpoint,
Demonstrating Statistically Significant Improvement in PFS



LOW
SURVIVAL
RATES

~9%
FIVE-YEAR
OVERALL
SURVIVAL
RATE

FEW
TREATMENT
OPTIONS

0
APPROVED
THERAPIES
FOR mIDH1
PATIENTS

POSITIVE
CLARIDHY
RESULTS

63%
REDUCTION IN
RISK OF DISEASE
PROGRESSION OR
DEATH FOR
PATIENTS
TREATED W/
TIBSOVO®



Global Phase 3 INDIGO Study of Vorasidenib in IDH Mutant Low-Grade Glioma

**SIGNIFICANT
2-HG
SUPPRESSION**

**IMPRESSIVE
PRELIMINARY
EFFICACY
DATA**

**ENCOURAGING
PHASE 1 DATA**

>90%

**2-HG
SUPPRESSION IN
RESECTED
MIDH1 GLIOMAS
ACROSS ALL
DOSES TESTED**

33% ORR

**IN THE
VORASIDENIB
ARM OF THE
PERIOPERATIVE
STUDY**

22 mo.

**MEDIAN
TREATMENT
DURATION IN
VORASIDENIB
PHASE 1**



**1:1 double-blind
randomization
(n=366)**

Stratified by 1p19q status
and baseline tumor size

**Vorasidenib
50 mg QD orally
Continuous 28-day cycles
(n=183)**

**Matched placebo*
(n=183)**

*centrally-confirmed progressive disease
will permit unblinding and crossover

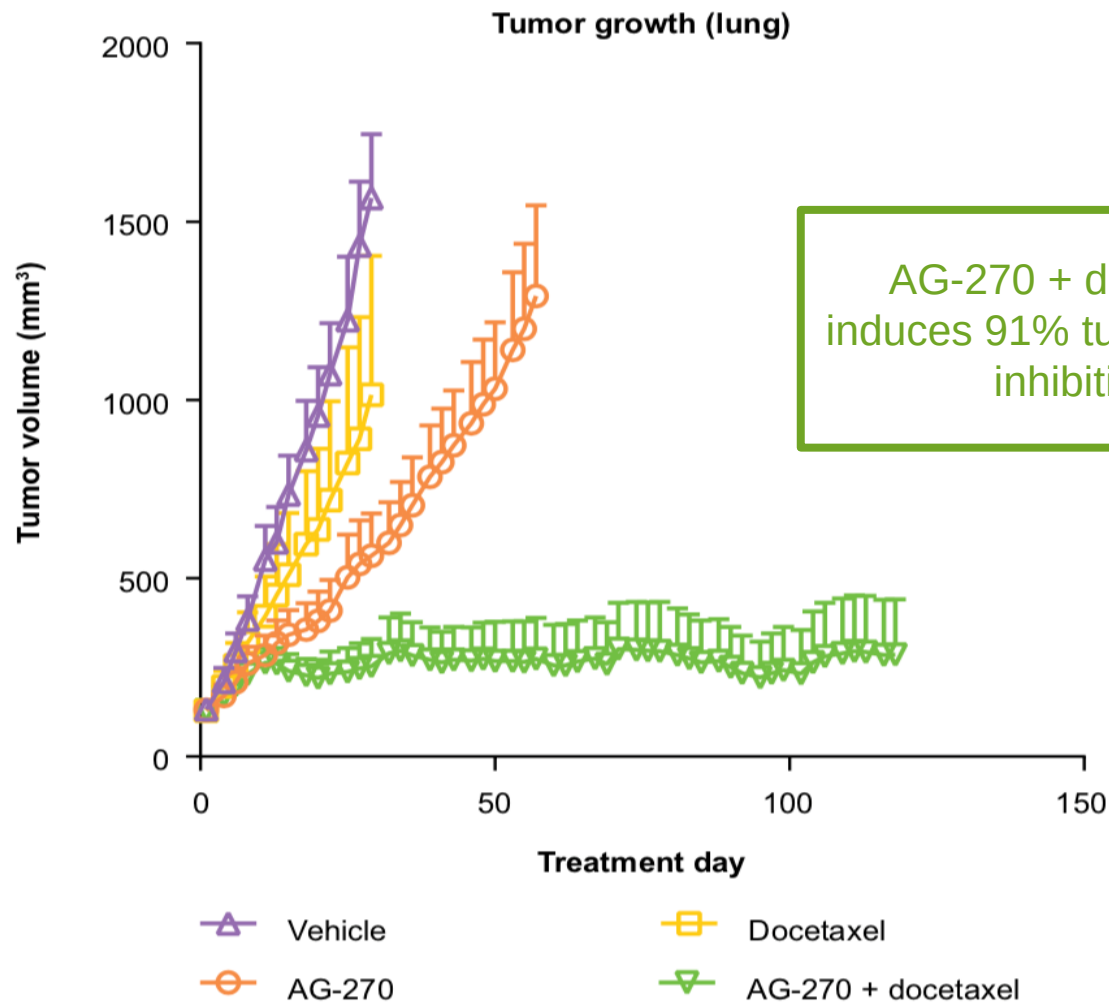
Endpoints

Primary: Progression free survival (by BIRC)

Secondary/Exploratory: Tumor volume, safety, ORR, OS, QOL, seizures, neuro-cognitive function, time to next intervention



AG-270, MAT2A Inhibitor, Preclinical Data Supports Combination with Taxanes; Two Phase 1 Combination Arms Ongoing



Source: Data presented at AACR-NCI-EORTC 2019

PHASE 1 COMBINATION ARMS INITIATED

AG-270 + docetaxel in
MTAP-deleted NSCLC
(2nd line)
N = up to 40

AG-270 + nab-paclitaxel
and gemcitabine in
MTAP-deleted pancreatic
ductal adenocarcinoma
(1st or 2nd line)
N = up to 45





CREATING MEDICINES IN THREE
FOCUS AREAS

1

Malignant Hematology

2

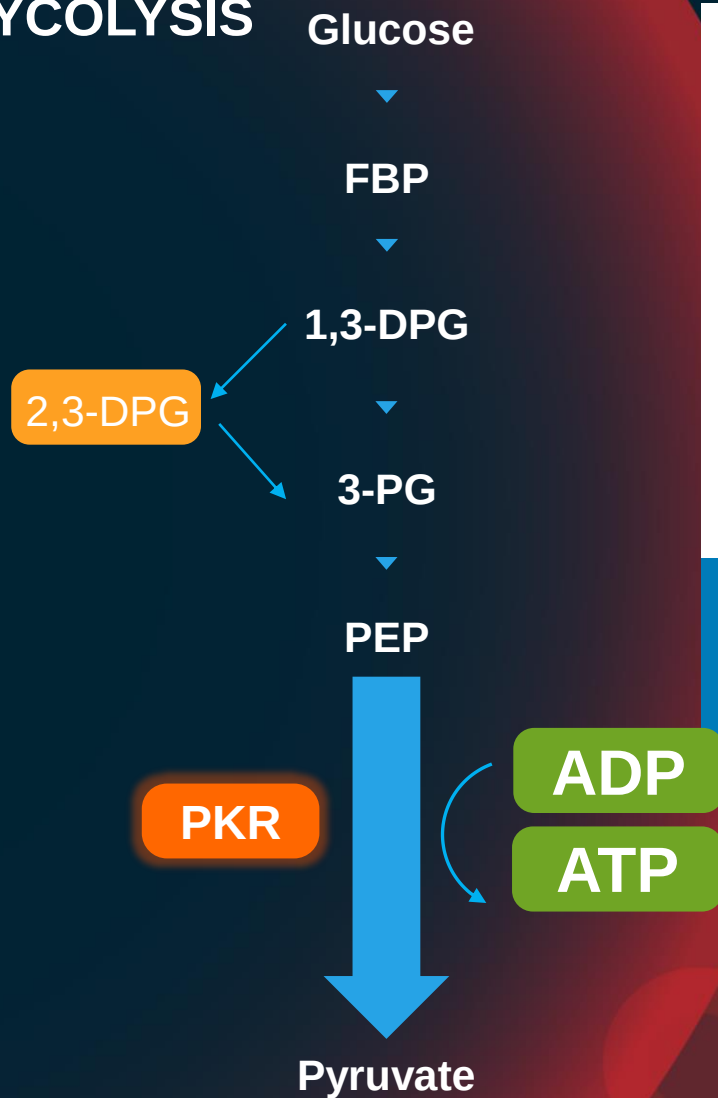
Solid Tumors

3

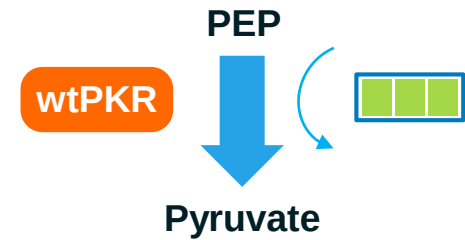
Rare Genetic Diseases

PKR Activation Represents Unique Mechanism of Action with Potential to Address Broad Range of Hemolytic Anemias

GLYCOLYSIS



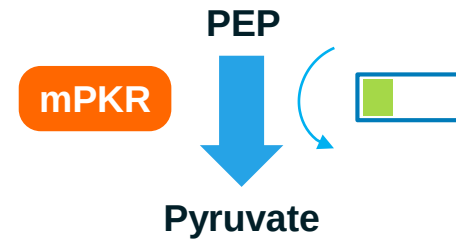
Normal Red Cell



Cellular Demand

ATP Production
Meets Demand

Mutant PKR Pyruvate Kinase Deficiency

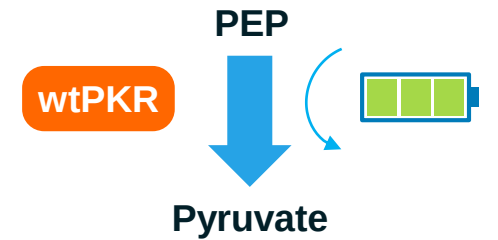


Cellular Demand

Inadequate
Production of ATP

- PKR mutations decrease PK stability, ATP generation and RBC membrane integrity and increase RBC destruction, leading to chronic hemolytic anemia

Wildtype PKR Other Hemolytic Anemias



Cellular Demand

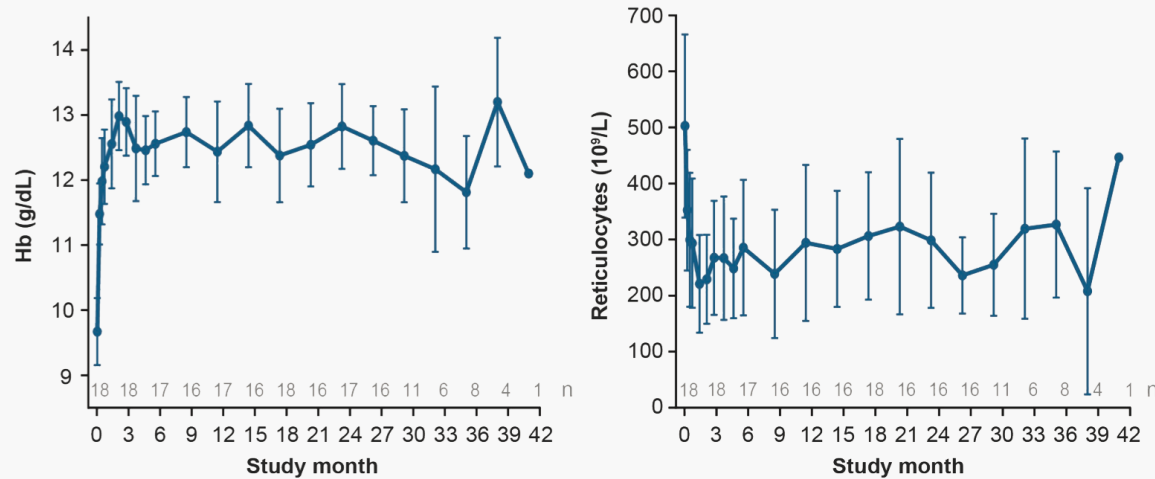
Increased
Demand of ATP

- In other hemolytic anemias, there is an increase in ATP demand and impaired ATP production, leading to damage and premature death of RBCs, hemolysis and anemia



Mitapivat has Potential to be First Disease-modifying Therapy for Patients with PK Deficiency

Improvements in Hemoglobin and Other Hemolysis Markers Maintained for More Than 3 Years in Responding Patients from DRIVE PK Extension



Chronic daily dosing with mitapivat for a median of 3 years and up to 42 months was well tolerated

COMPLICATIONS & COMORBIDITIES REGARDLESS OF TRANSFUSION STATUS

HIGHER LIFETIME RATES OF PULMONARY HYPERTENSION, OSTEOPOROSIS, AND LIVER CIRRHOSIS

SUPPORTIVE CARE ONLY

0 APPROVED THERAPIES

HIGH RISK OF IRON OVERLOAD

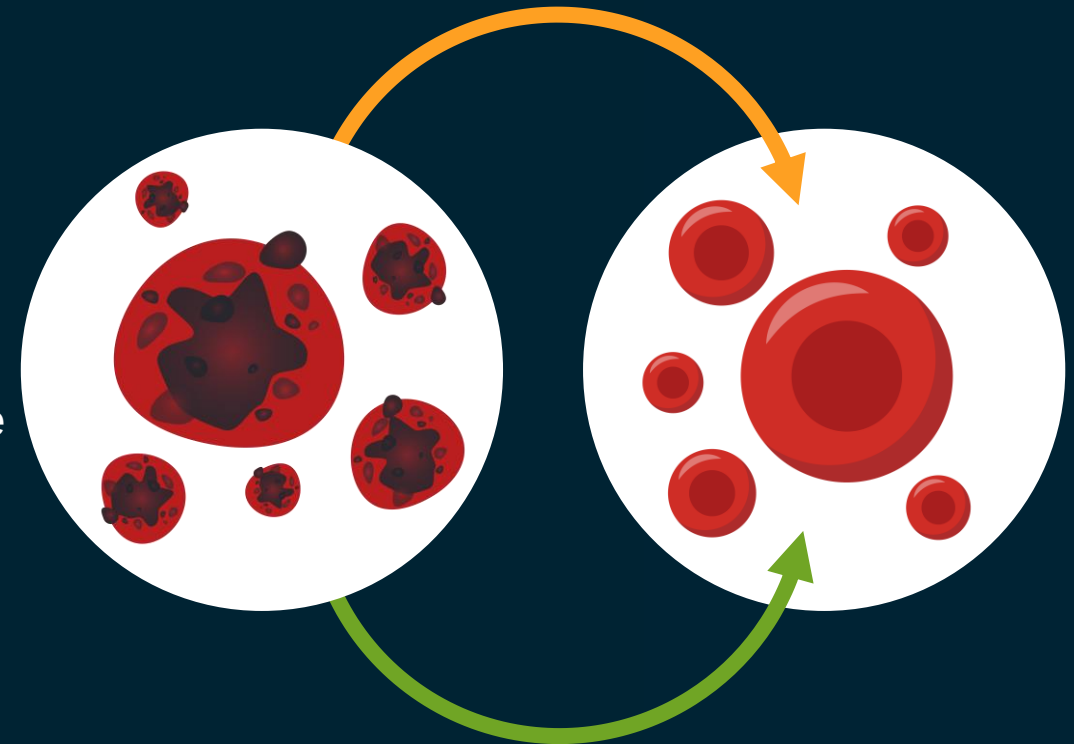
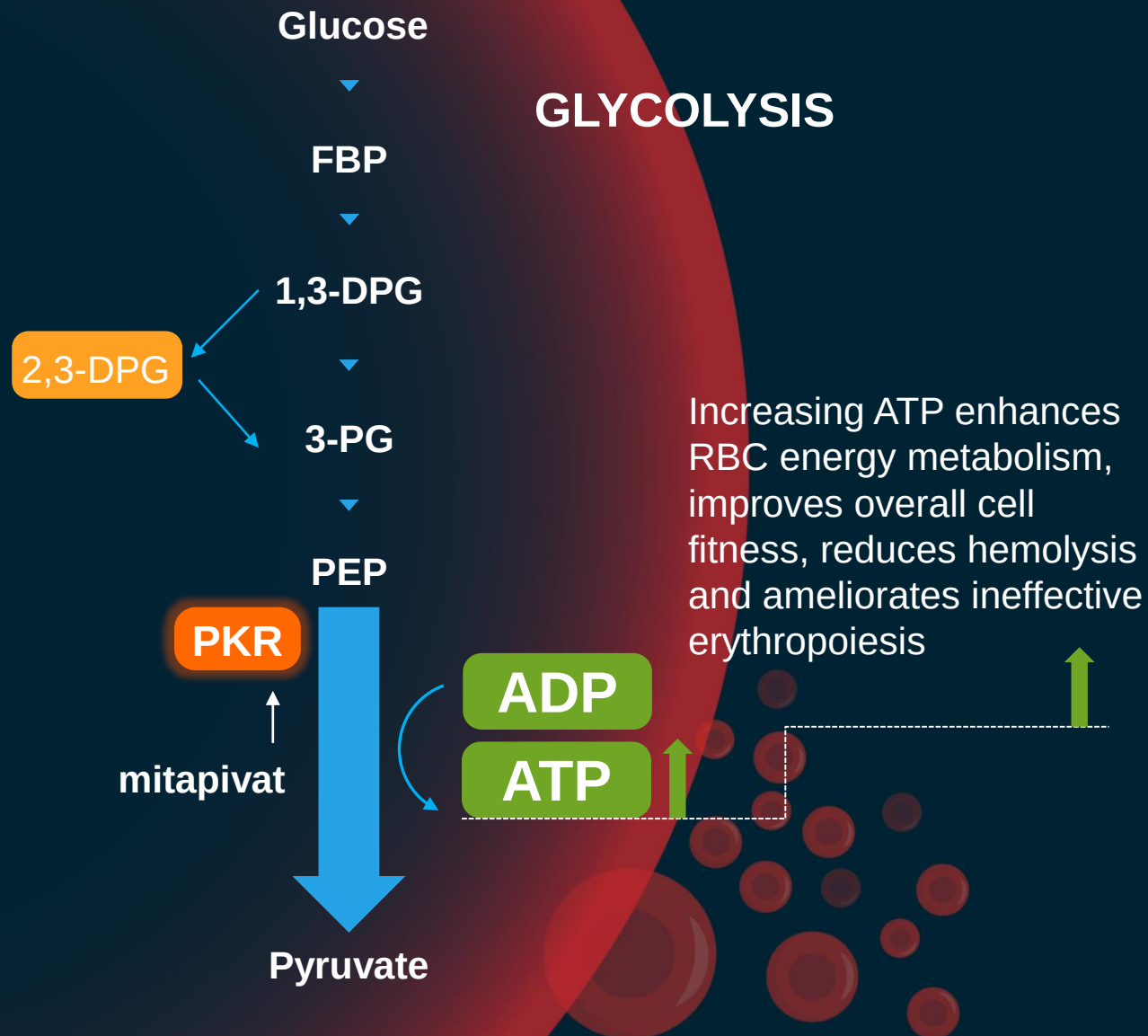
38% OF PATIENTS NOT RECEIVING REGULAR TRANSFUSIONS EXPERIENCE IRON OVERLOAD

Source: Data presented at ASH 2019; van Beers EJ, et al. Haematologica. 2019;104(2):e51-e53.

Topline data from ACTIVATE and ACTIVATE-T expected between YE 2020 and mid-2021



PKR Activators May Improve Thalassemic RBC Production and Survival by Increasing ATP Production



Study Design: Open-label, Phase 2, Multi-center Trial of Mitapivat in Thalassemia

Key Inclusion Criteria

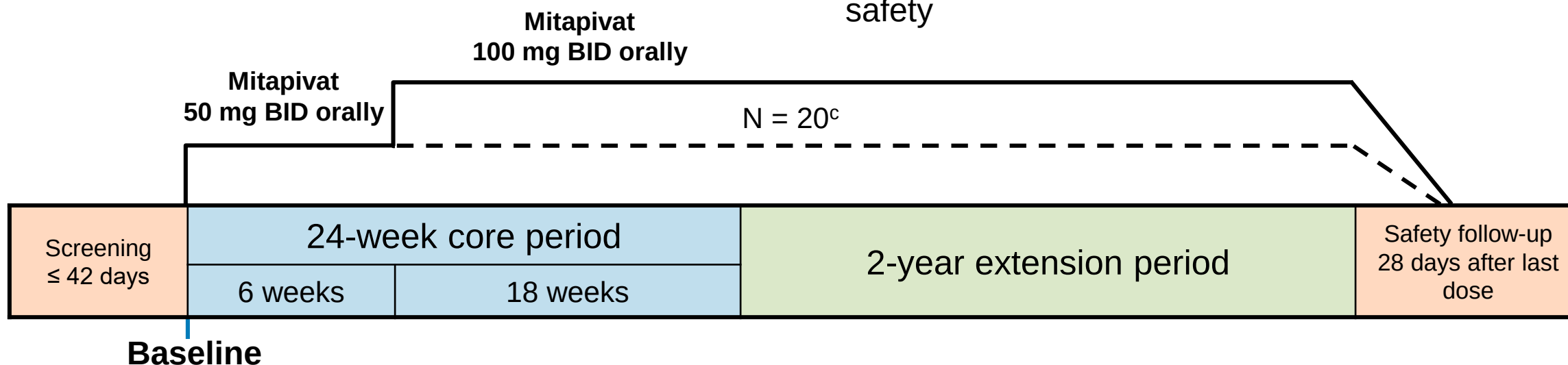
- β -thalassemia $\pm$ α -globin gene mutations, HbE β -thalassemia, or α -thalassemia (HbH disease)
- Hb $\leq$ 10.0 g/dL
- Non-transfusion-dependent^a

Primary Endpoint^b

- Hb response, defined as increase of $\geq$ 1.0 g/dL from baseline at any time between weeks 4–12, inclusive

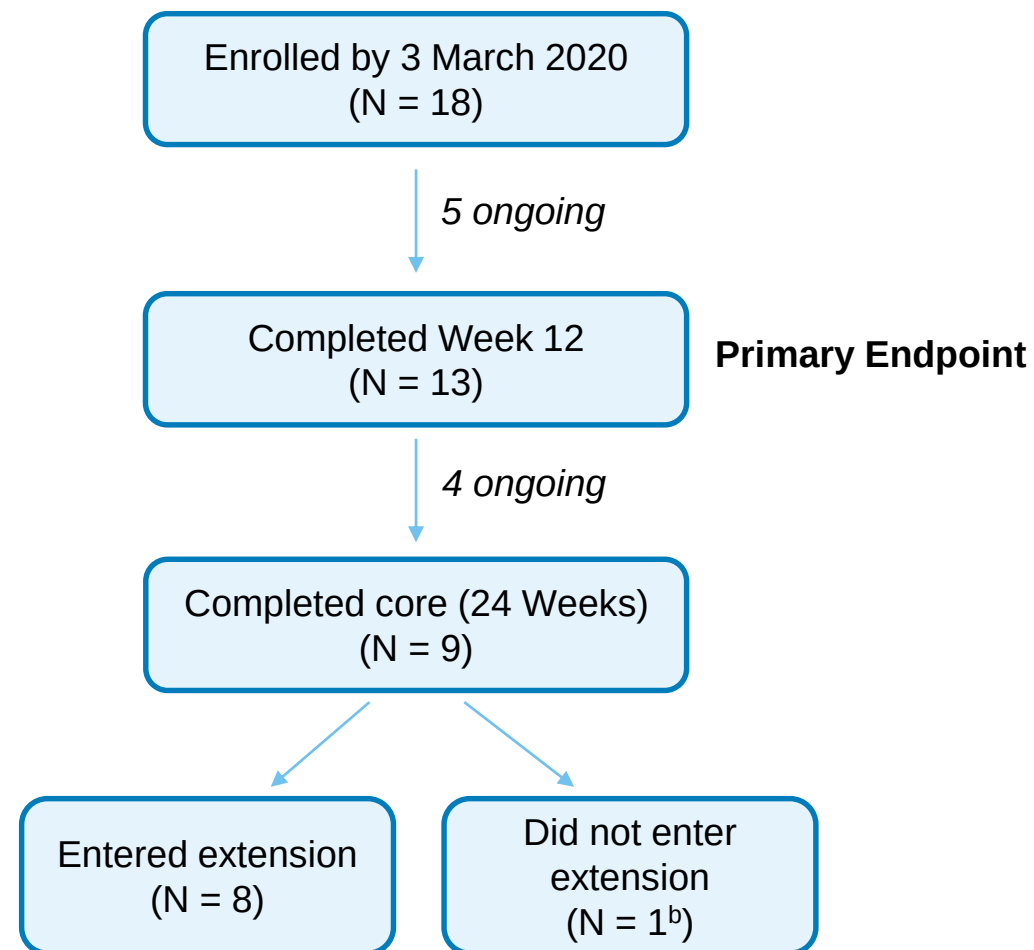
Secondary/Exploratory Endpoints

- Sustained Hb response; delayed Hb response; markers of hemolysis; hematopoietic activity; safety



Demographics and Disposition

Baseline characteristics	Total (N = 18)
Median (range) duration of treatment, weeks	20.6 (1.1–50.0)
Male/female, n	5/13
Age at informed consent, median (range), years	43.5 (29–67)
Race, n (%)	
Asian	9 (50.0)
White	4 (22.2)
Native Hawaiian or other Pacific Islander	1 (5.6)
Other ^a	4 (22.2)
Thalassemia type, n (%)	
α	5 (27.8)
β	13 (72.2)
Hb baseline, median (range), g/dL	8.43 (5.6–9.8)
Indirect bilirubin, median (range), mg/dL	1.17 (0.31–5.52)
Lactate dehydrogenase, median (range), U/L	249 (126–513)
Erythropoietin, median (range), mU/mL	70.5 (15–11,191)



Interim Phase 2 Results in Thalassemia: Primary Endpoint Met in 92.3% of Patients

Endpoint	Genotype	N/N	%	90% CI
Hb responders during weeks 4–12 among those who completed 12 weeks	All	12/13	92.3	68.4, 99.6
	α	4/4	100	47.3, 100
	β	8/9	88.9	57.1, 99.4
Hb responders during weeks 12–24 among those who completed 24 weeks	β^a	8/9	88.9	57.1, 99.4
Sustained responders: primary response and ≥ 2 Hb responses during weeks 12–24	β^a	7/8	87.5	52.9, 99.4

Patient population	N	Weeks	Mean (SD) change from baseline Hb, g/dL
All patients	13	4–12	1.34 (0.7)
α -thalassemia	4	4–12	1.17 (0.4)
β -thalassemia	9	4–24	1.43 (0.8)
β -thalassemia responders	8	4–24	1.63 (0.5)
All responders	12	4–12	1.47 (0.5)

Hb responder defined as a ≥ 1.0 g/dL Hb increase from baseline at least once; Only patients with β -thalassemia had completed 24 weeks of treatment at the time of datacut; data presented at EHA 2020



Interim Phase 2 Results in Thalassemia: Activation of wPKR by Mitapivat Improved Hb and Associated Markers of Hemolysis and Erythropoiesis

Treatment with mitapivat induced Hb increase of ≥ 1.0 g/dL in 12 of 13 evaluable patients, including 4 of 4 α -thalassemia patients; 7 of 8 evaluable patients achieved sustained Hb response
Median (range) time to Hb increase of ≥ 1 g/dL among responders was 3.1 (1.4–7.1) weeks

Mitapivat was generally well tolerated; the safety profile was consistent with previous studies

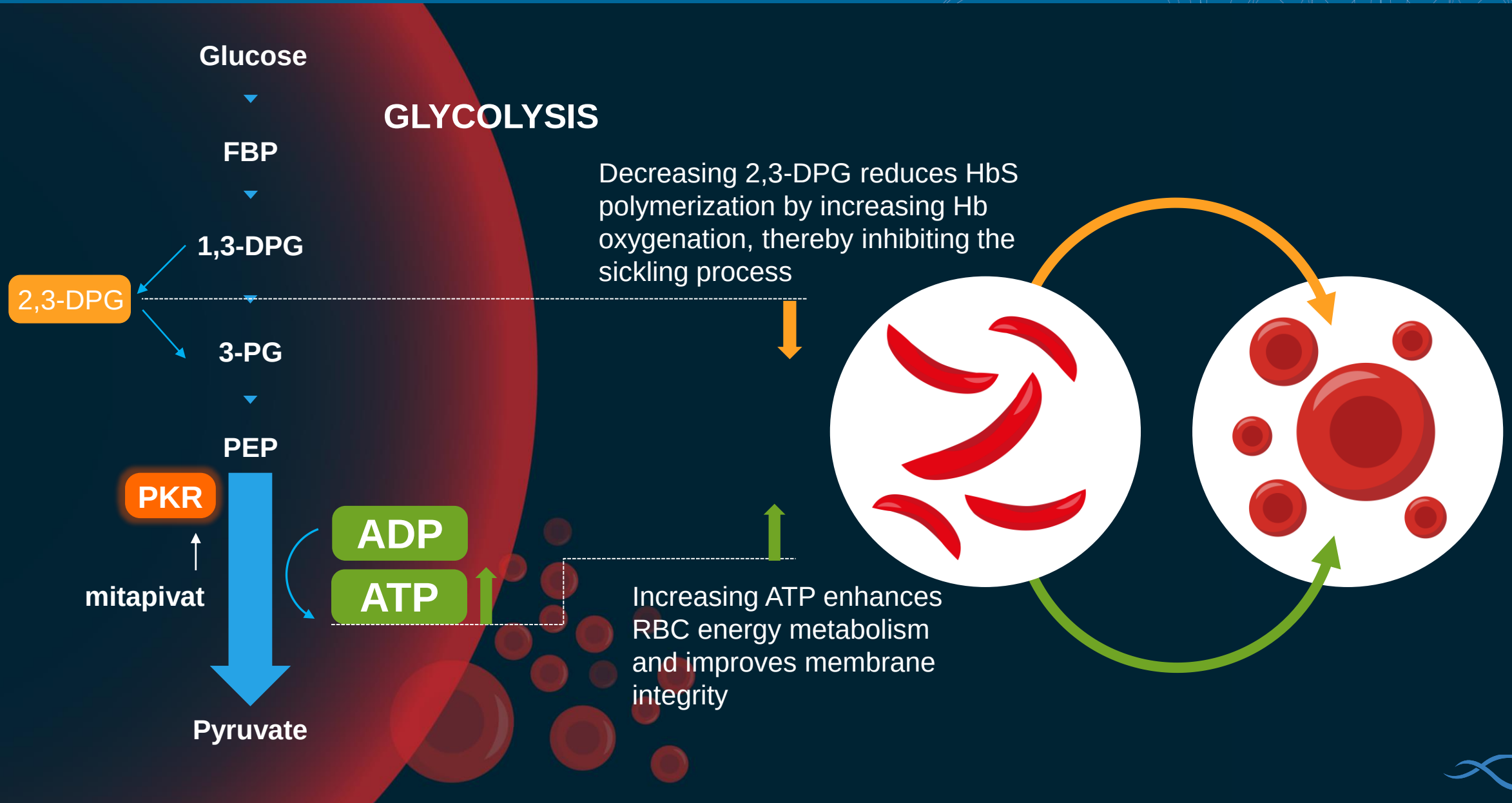
Improvements in markers of hemolysis and erythropoiesis correlated with the Hb increases

Mean ATP percent increase from baseline was similar to that previously observed with mitapivat in healthy volunteers

Pivotal plan for mitapivat in α - and β -thalassemia expected to be finalized by year-end 2020 and initiated in 2021



PKR Activation in Sickle Cell Disease Modulates 2,3-DPG and ATP to Potentially Improve Anemia and Reduce Sickling



NHLBI & Agios CRADA Study of Mitapivat in SCD: Study Design

Primary

Safety and tolerability

- Frequency and severity of adverse events
- Changes in laboratory parameters (including reticulocyte counts and levels of hemoglobin, bilirubin, and lactate dehydrogenase)

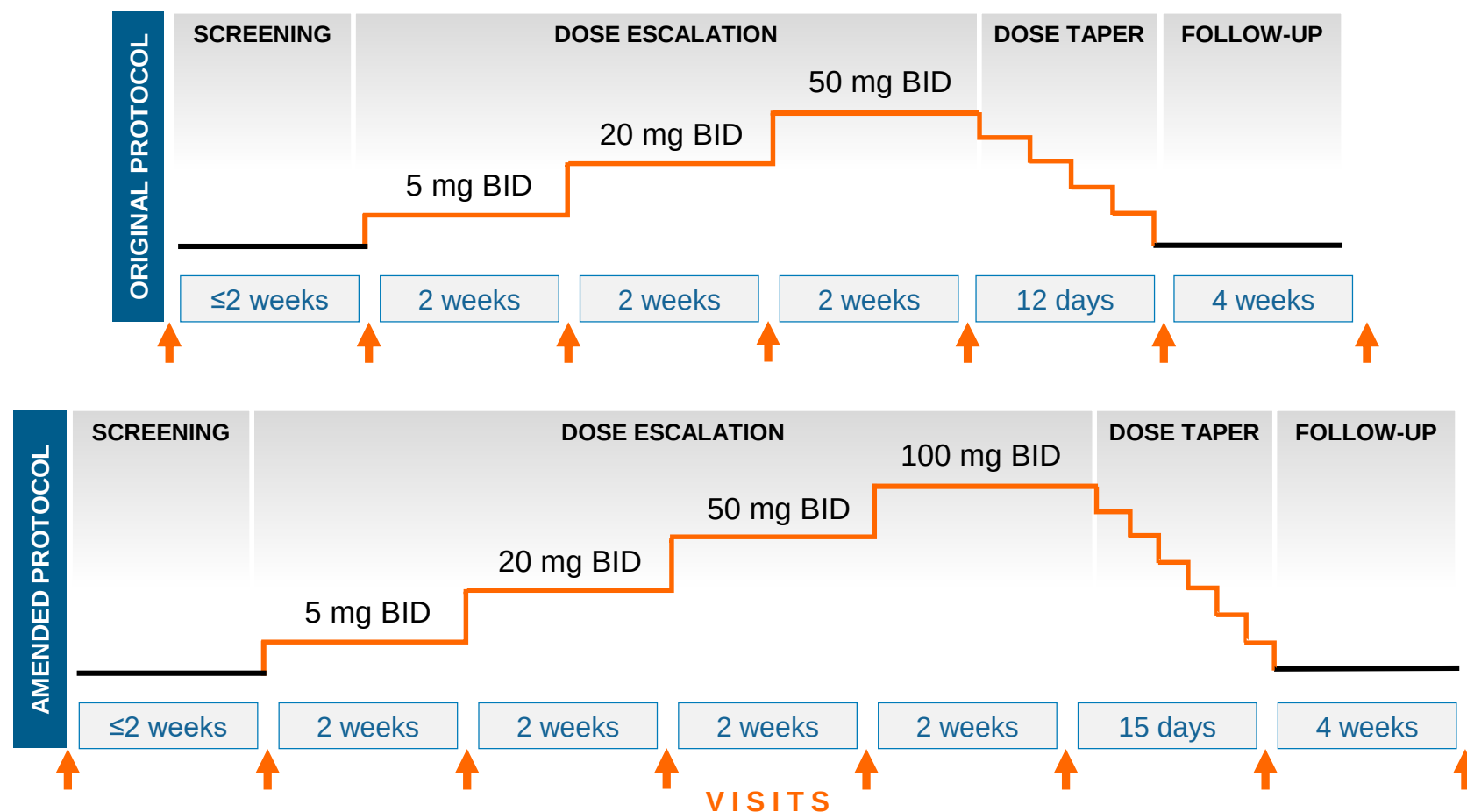
Secondary

Pharmacokinetics/pharmacodynamics

- Pharmacokinetics of mitapivat (AG-348)
- Levels of 2,3-DPG, PK-R, and ATP, and oxygen dissociation sickling in RBCs
- Relationship between mitapivat pharmacokinetics and safety

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Escalating Multiple Oral Doses of Mitapivat in Subjects With Stable SCD

ClinicalTrials.gov NCT04000165: Nonrandomized, open-label, phase 1 study; N ≈ 15–25



Clinical Proof-of-concept for Mitapivat Established in Sickle Cell Disease

7 of 8 (88%) efficacy evaluable patients experienced a Hb increase, and 5 of 8 (63%) patients achieved a Hb increase of ≥ 1.0 g/dL from baseline (range 1.0-2.7 g/dL) at doses of 50 mg BID or lower

Treatment with mitapivat was associated with decreases in hemolytic markers such as bilirubin, LDH and reticulocytes

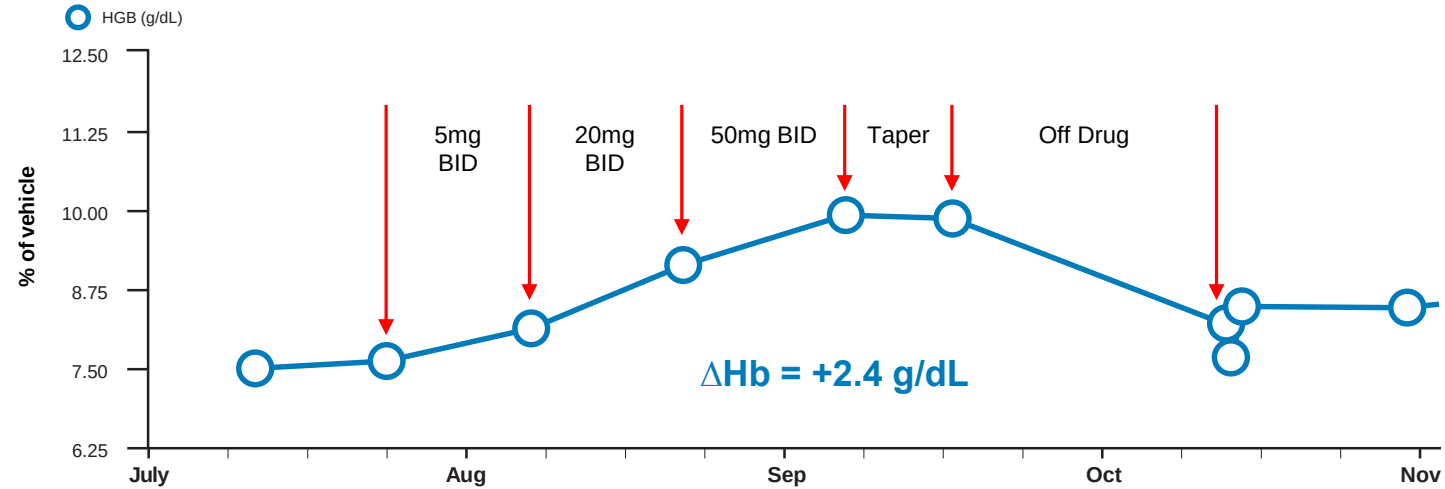
2,3-DPG decreases and increases in ATP levels were observed. Sickling curves (t50) and oxygen dissociation curves (p50) consistent with decreases in both sickling and HbS polymerization

AEs generally consistent with previously reported data with mitapivat treatment or are to be expected in the context of SCD. One SAE, a VOC, occurred during drug taper and was possibly attributed to mitapivat.

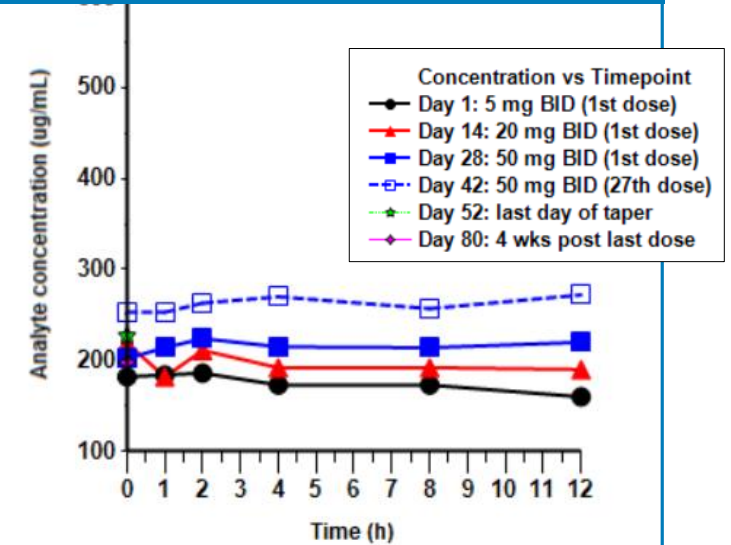


Illustrative Sick Cell Patient Case Study: Male, 39 Years Old

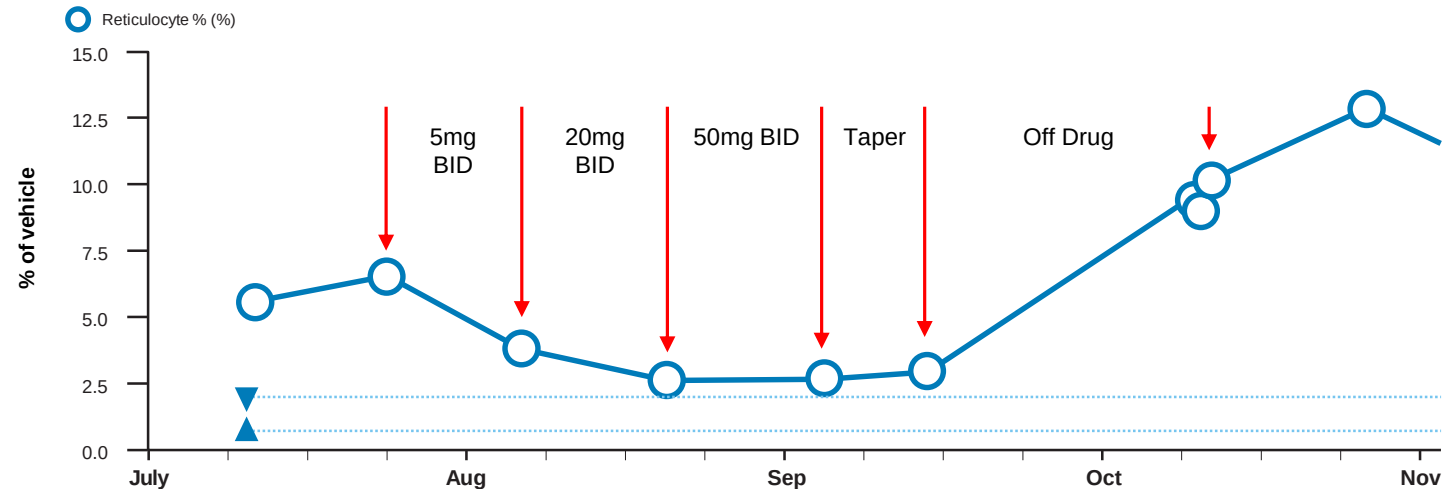
HEMOGLOBIN



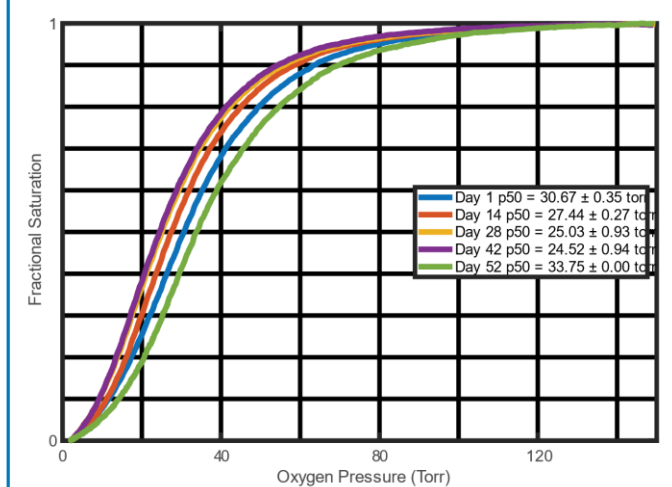
ATP



RETICULOCYTE %



OXYGEN PRESSURE



PKR Activation Has Potential Broad Utility Across Hemolytic Anemias

~3-8K
PATIENTS IN
U.S. & EU

Pyruvate Kinase Deficiency

NTD Adult PKD	Phase 3 enrollment complete; Topline data expected YE 2020 – mid 2021
TD Adult PKD	Phase 3 enrollment complete; Topline data expected YE 2020 – mid 2021
Pediatric PKD	Pivotal plan expected by YE

**~18-
23K**
PATIENTS IN
U.S. & EU

β- and α-Thalassemia

NTD β- and α-Thalassemia	Phase 2 enrollment complete
Thalassemia	Pivotal plan expected by YE and initiation in 2021

**~120-
135K**
PATIENTS IN
U.S. & EU

Sickle Cell Disease

Adult SCD	NIH CRADA; data to be submitted to ASH
Adult SCD	Pivotal study expected to initiate in 2021





CREATING MEDICINES IN
THREE FOCUS AREAS

1

Malignant Hematology

2

Solid Tumors

3

Rare Genetic Diseases

Second Quarter 2020 Financial Results

Statement of Operations	Three Months Ended 6/30/20	Three Months Ended 6/30/19
Total Revenue	\$37.3M	\$26.2M
Collaboration Revenue	6.4M	9.8M
TIBSOVO® Net Sales	27.6M	13.7M
Royalty Revenue	3.3M	2.7M
Cost of Sales	0.7M	0.3M
Research & Development Expense	90.9M	107.4M
Selling, General & Administrative Expense	36.0M	32.4M

Balance Sheet	6/30/20	12/31/19
Cash, Cash Equivalents and Marketable Securities	\$794M	\$718M

June 30, 2020 cash balance provides runway through the end of 2022





AGIOS 2025 VISION:

Focused Innovation. Ambitious Development.
Transformative Treatments for Patients Across Three Focus Areas.

4

MEDICINES

8+

INDICATIONS

6+

**MOLECULES
IN THE CLINIC**

\$

**CASH FLOW
POSITIVE**