agios

AGIOS

August 2020

Cautionary Statements

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."

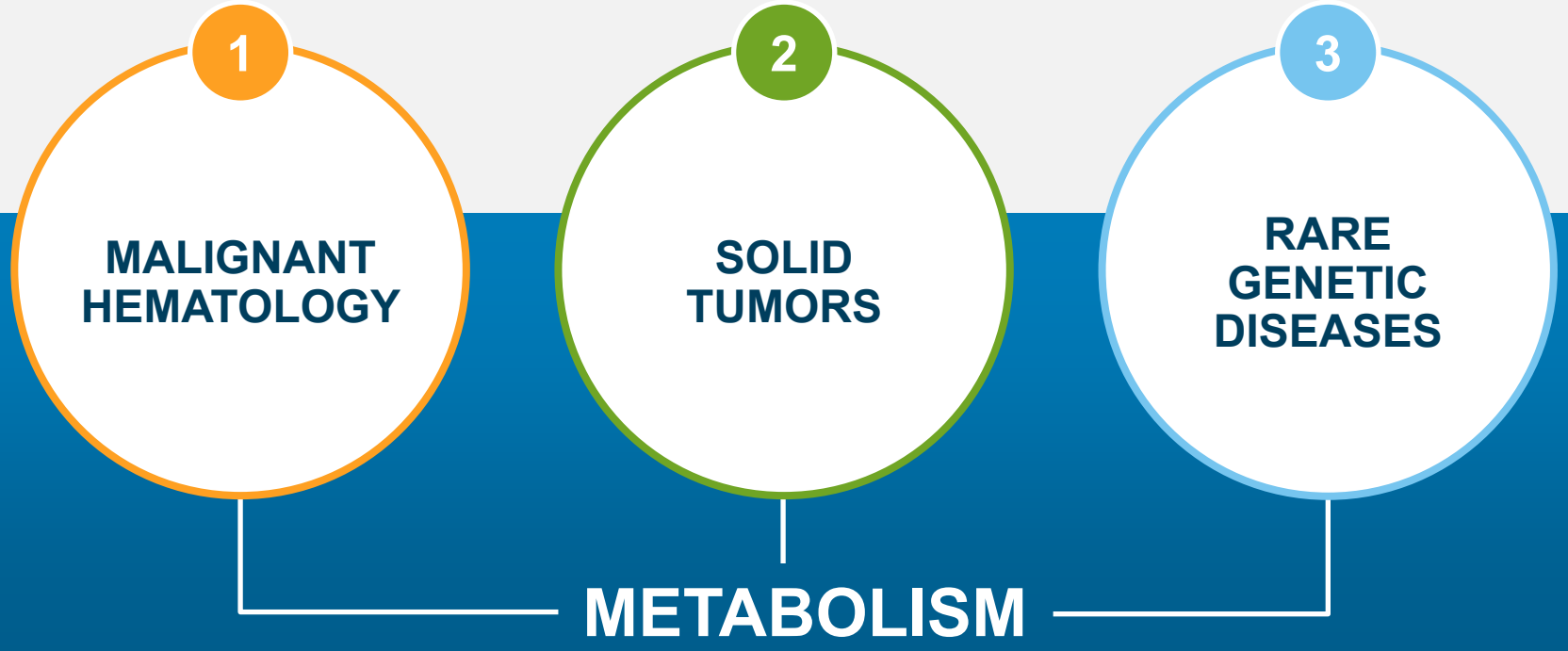
—Tamara S., Minnesota

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

LEARN MORE AT KNOWPKDEFICIENCY.COM

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

10 YEARS

Productive Research Engine	Creative Clinical Development	Patient-centric Approach	"Other Side Of Possible" Culture
8 INVESTIGATIONAL NEW DRUG CANDIDATES	**70+** PEER-REVIEWED PUBLICATIONS	**10+** RESEARCH PROGRAMS	**1,500+** PATIENTS TREATED IN OUR CLINICAL TRIALS

2 MEDICINES APPROVED **+ 4** ADDITIONAL MOLECULES IN CLINICAL DEVELOPMENT

~550

HIGH CALIBER EMPLOYEES WITH 1 VISION

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

	NOW	2025
COMMERCIAL	2 MEDICINES	4 MEDICINES
LABEL EXPANSION	2 INDICATIONS	8+ INDICATIONS
PRODUCTIVE DISCOVERY ENGINE	4 MOLECULES IN THE CLINIC	6+ MOLECULES IN THE CLINIC
FINANCIAL	$105-115M EXPECTED U.S. TIBSOVO® 2020 REVENUE	CASH FLOW POSITIVE

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

agios

CREATING MEDICINES IN THREE FOCUS AREAS

1. Malignant Hematology
2. Solid Tumors
3. Rare Genetic Diseases

agios

CREATING MEDICINES IN THREE FOCUS AREAS

1. Malignant Hematology
2. Solid Tumors
3. 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.

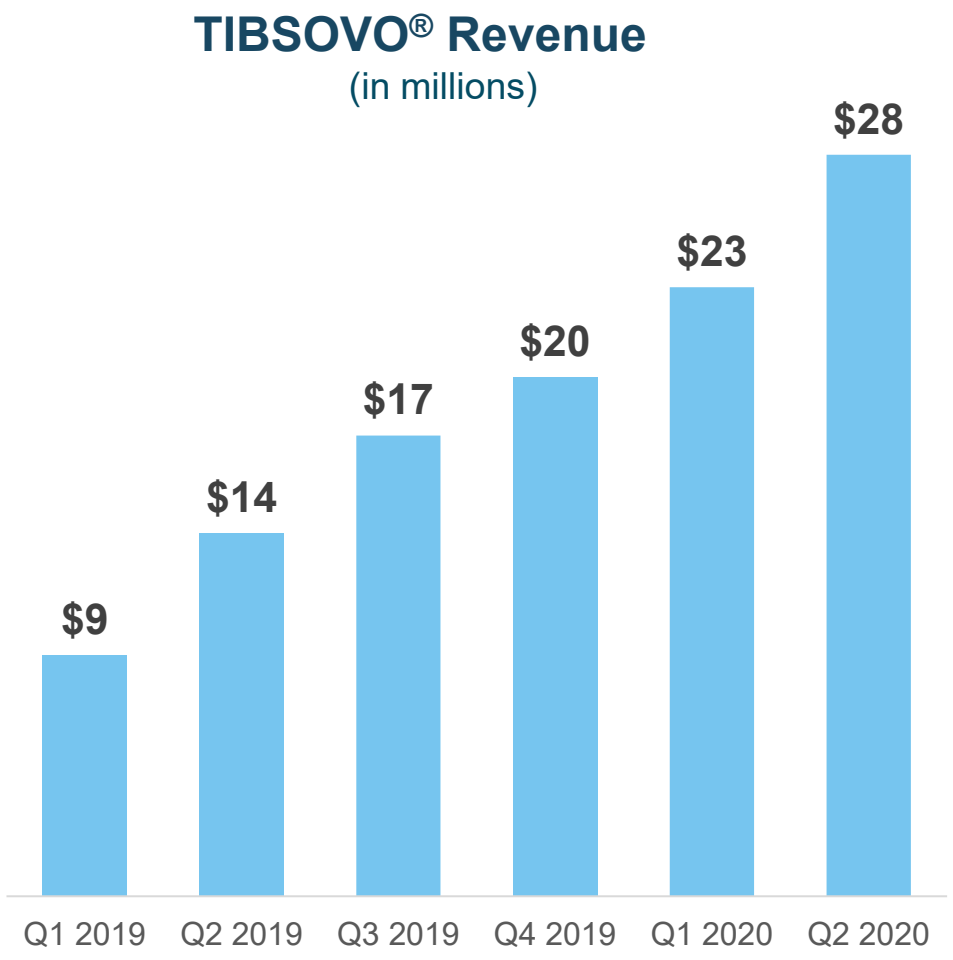
IDH1 Mutant Myelodysplastic Syndrome (MDS)

TIBSOVO®

R/R MDS	Phase 1 Expansion

Source: Agios estimates, market research, SEER, MDS Foundation, Datamonitor

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

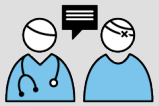


22% Growth

In Product Revenue Quarter-over-Quarter

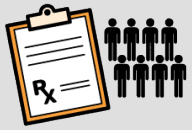
$105 – 115M

U.S. Net Sales Guidance for 2020



15% Increase

In Unique Prescribers Quarter-over-Quarter



~1,600

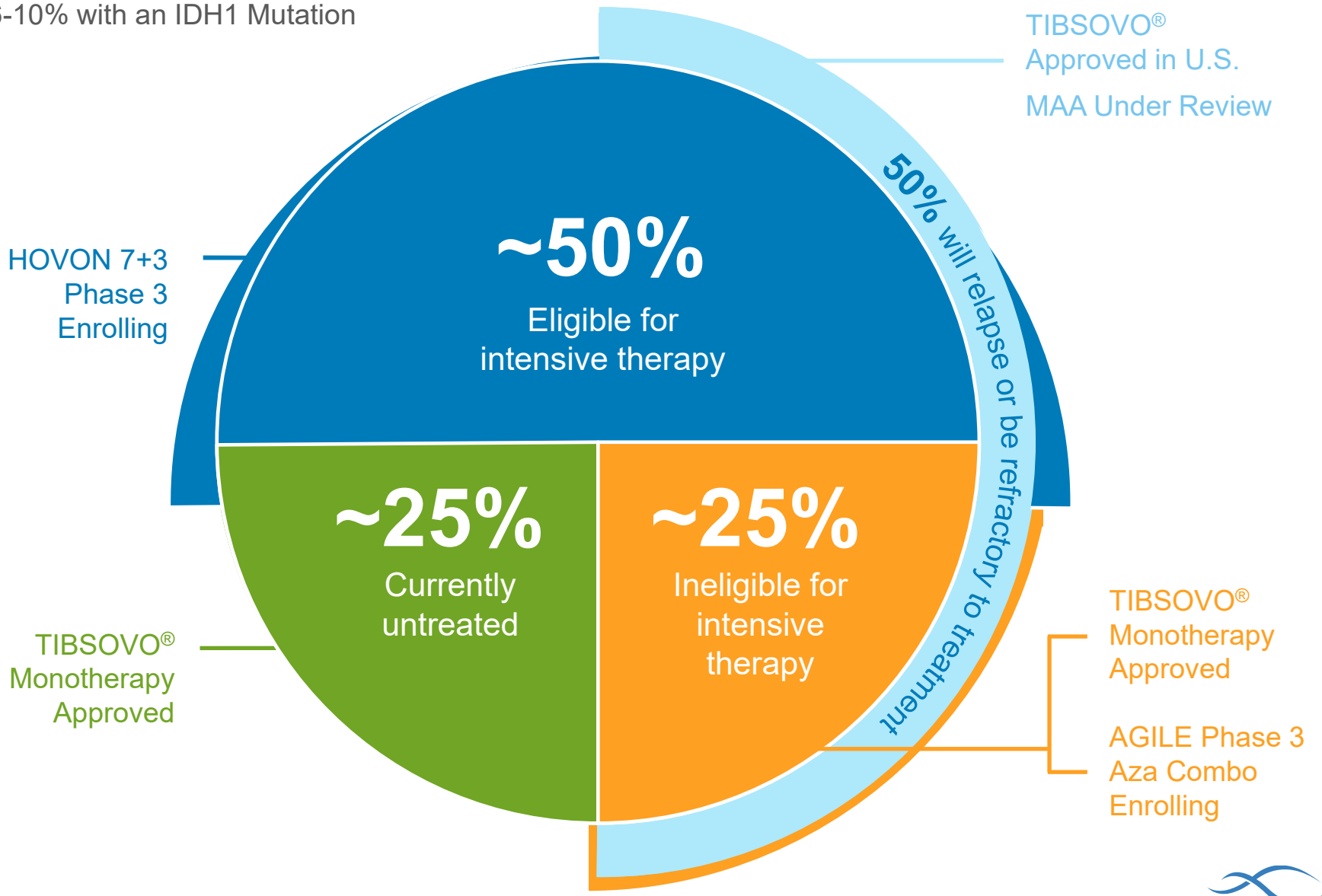
Patients Treated Since Launch

Source: Agios estimates

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

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

6-10% with an IDH1 Mutation



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

agios

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

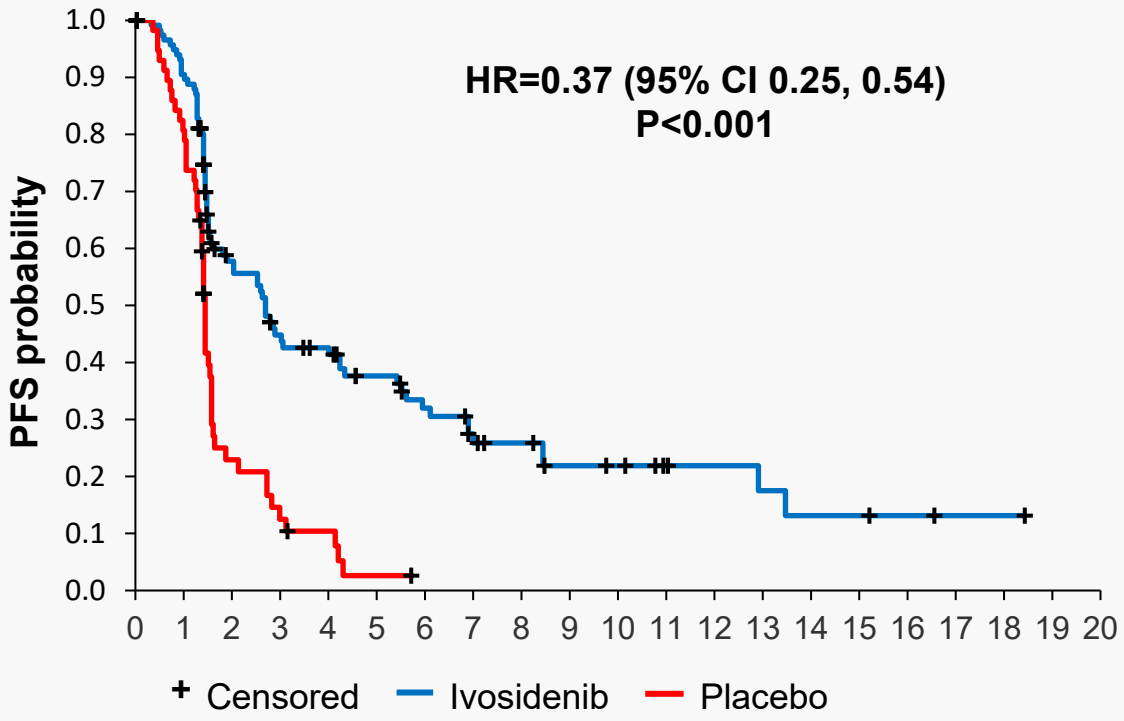
1st or 2nd Line Pancreatic Cancer	Phase 1 Combo

Source: Agios estimates, market research

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®

Sources: CDC National Program of Cancer Registries (NPCR); Epiphany Partners Epic Oncology; Decision Resources; Market Research; Borger DR et al. Oncologist 2012;17:72-9.; Kipp BR et al. Hum Pathol 2012;43:1552-8.; Goyal L et al. Oncologist 2015;20:1019-27; data from ESMO 2019

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

SIGNIFICANT 2-HG SUPPRESSION

>90%

2-HG SUPPRESSION IN RESECTED mIDH1 GLIOMAS ACROSS ALL DOSES TESTED

IMPRESSIVE PRELIMINARY EFFICACY DATA

33% ORR

IN THE VORASIDENIB ARM OF THE PERIOPERATIVE STUDY

ENCOURAGING PHASE 1 DATA

22 mo.

MEDIAN TREATMENT DURATION IN VORASIDENIB PHASE 1

INDIGO | INVESTIGATING VORASIDENIB IN GLIOMA

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

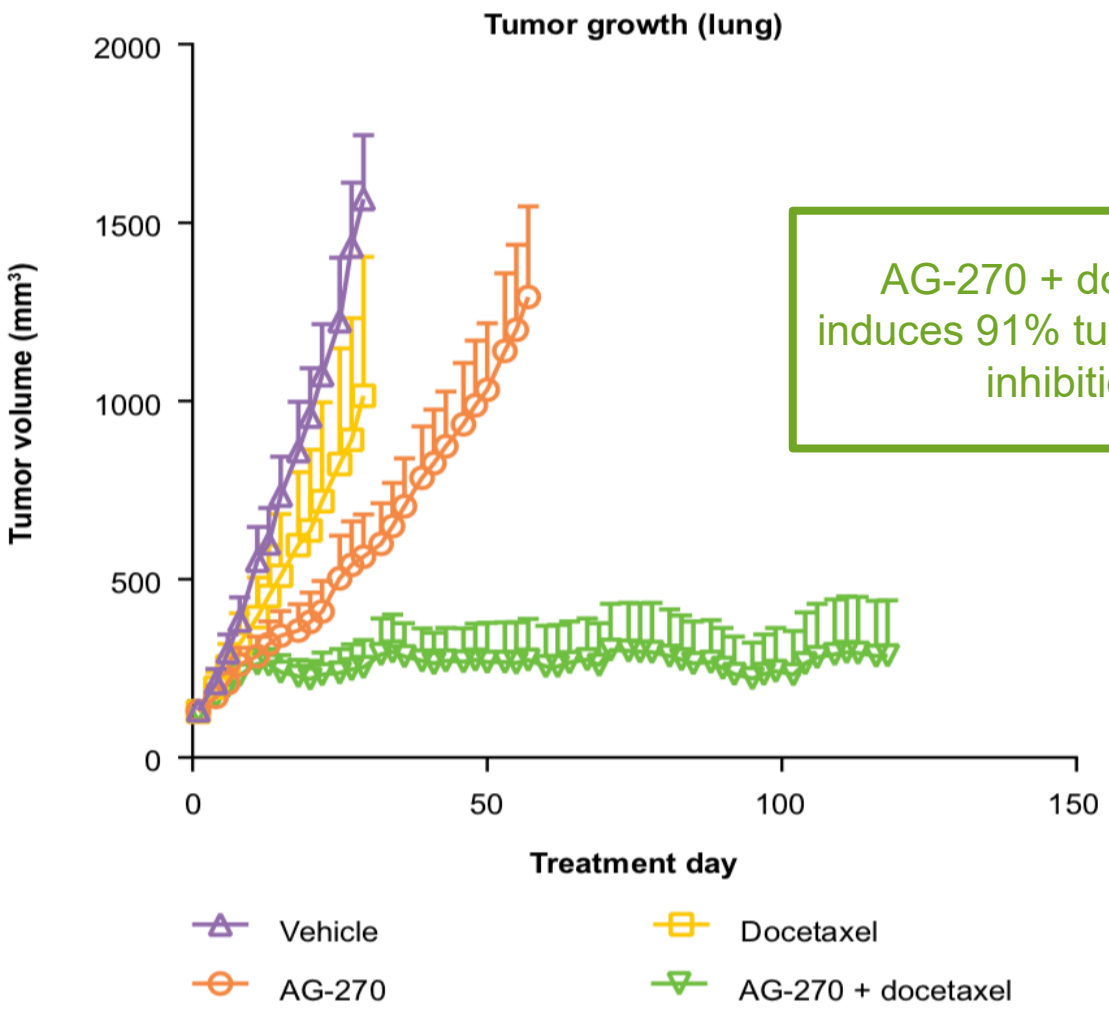
Endpoints

Primary: Progression free survival (by BIRC)

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

BIRC = blinded independent review committee, ORR = overall response rate, OS = overall survival, QOL = quality of life, WHO = World Health Organization; Source: Data presented at SNO 2019

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



AG-270 + docetaxel induces 91% tumor growth inhibition

4 of 8 animals were tumor free at last dose and remained tumor free until the arm was terminated on Day 141

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

Modest near-term investment to enable pivotal strategy decision by YE2022

agios

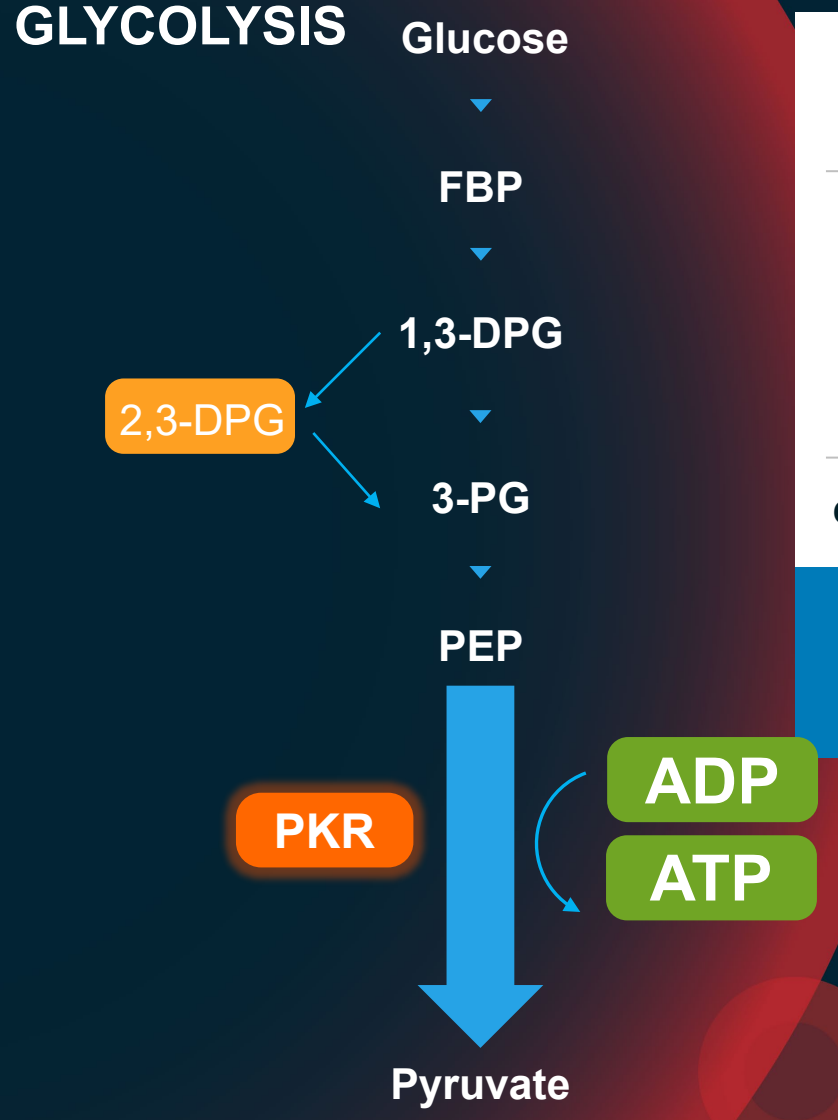
CREATING MEDICINES IN THREE FOCUS AREAS

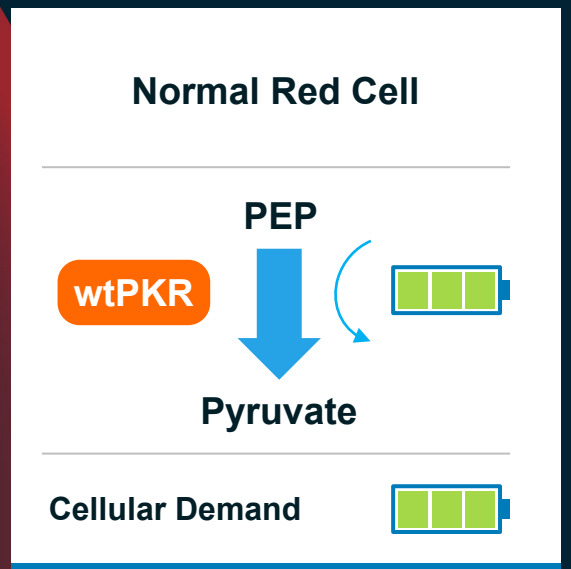
1 Malignant Hematology

2 Solid Tumors

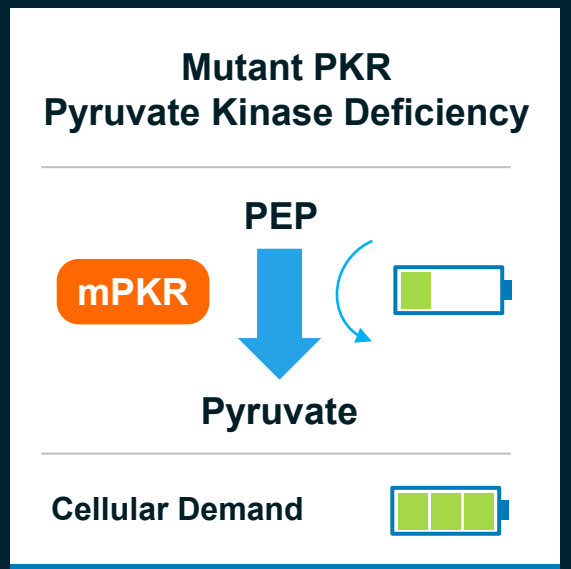
3 Rare Genetic Diseases

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



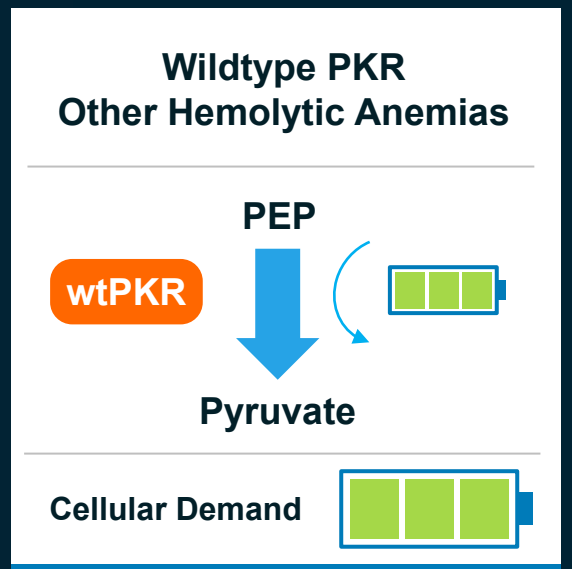


ATP Production Meets Demand



Inadequate Production of ATP

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

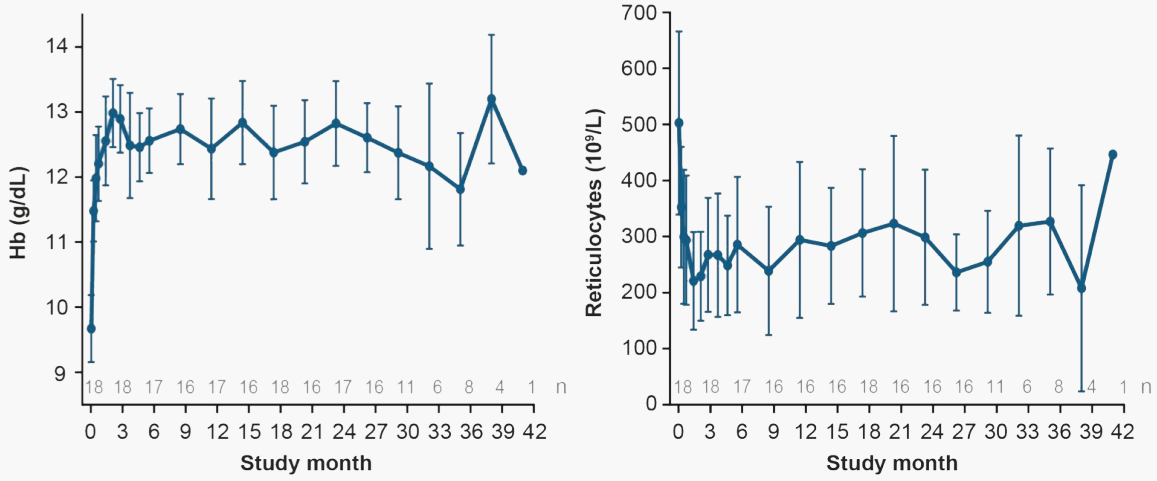


Increased Demand of ATP

- 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



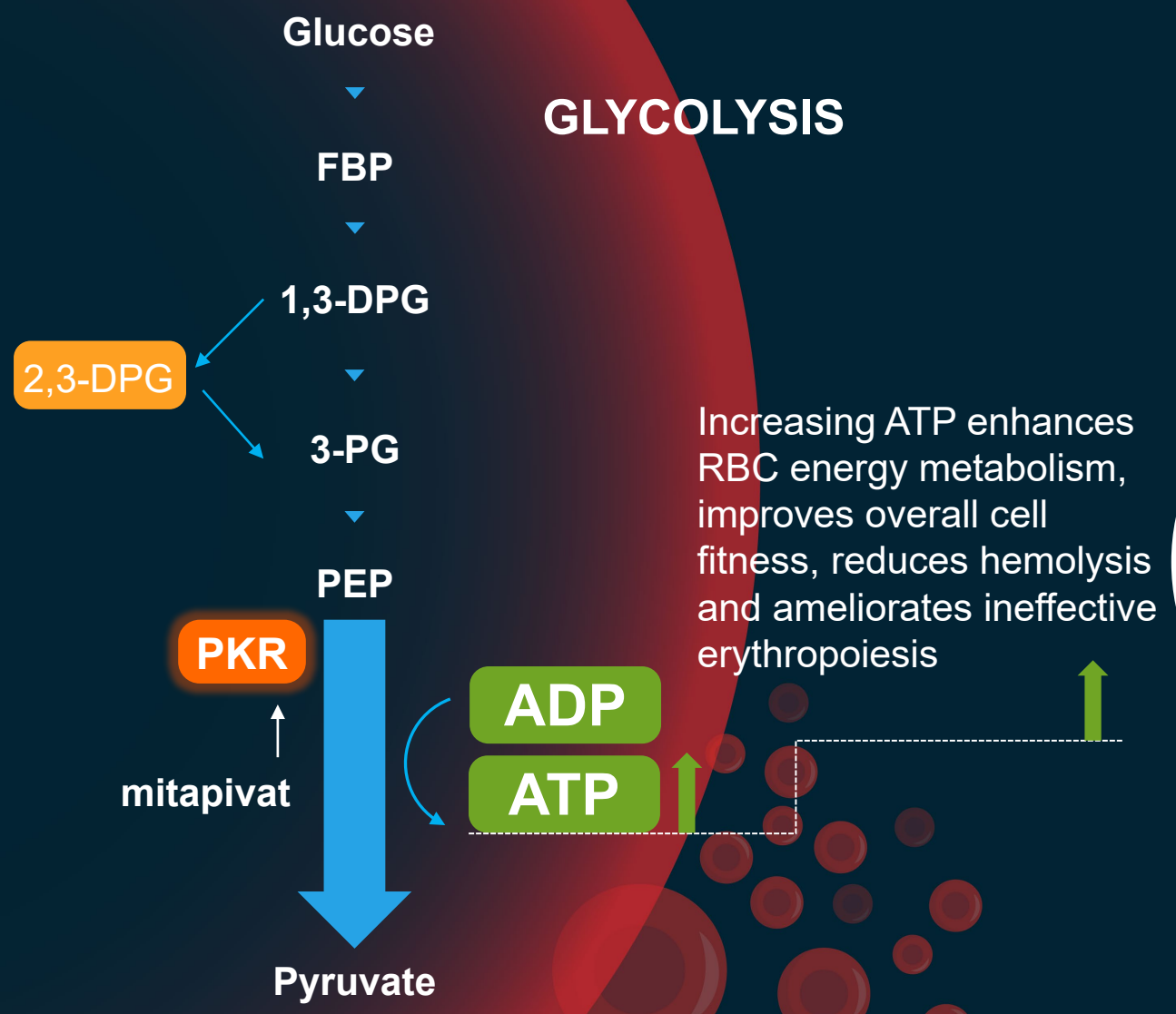
Chronic daily dosing with mitapivat for a median of 3 years and up to 42 months was well tolerated

COMPLICATIONS & COMORBIDITIES REGARDLESS OF TRANSFUSION STATUS	SUPPORTIVE CARE ONLY	HIGH RISK OF IRON OVERLOAD
HIGHER LIFETIME RATES OF PULMONARY HYPERTENSION, OSTEOPOROSIS, AND LIVER CIRRHOSIS	0 APPROVED THERAPIES	38% OF PATIENTS NOT RECEIVING REGULAR TRANSFUSIONS EXPERIENCE IRON OVERLOAD

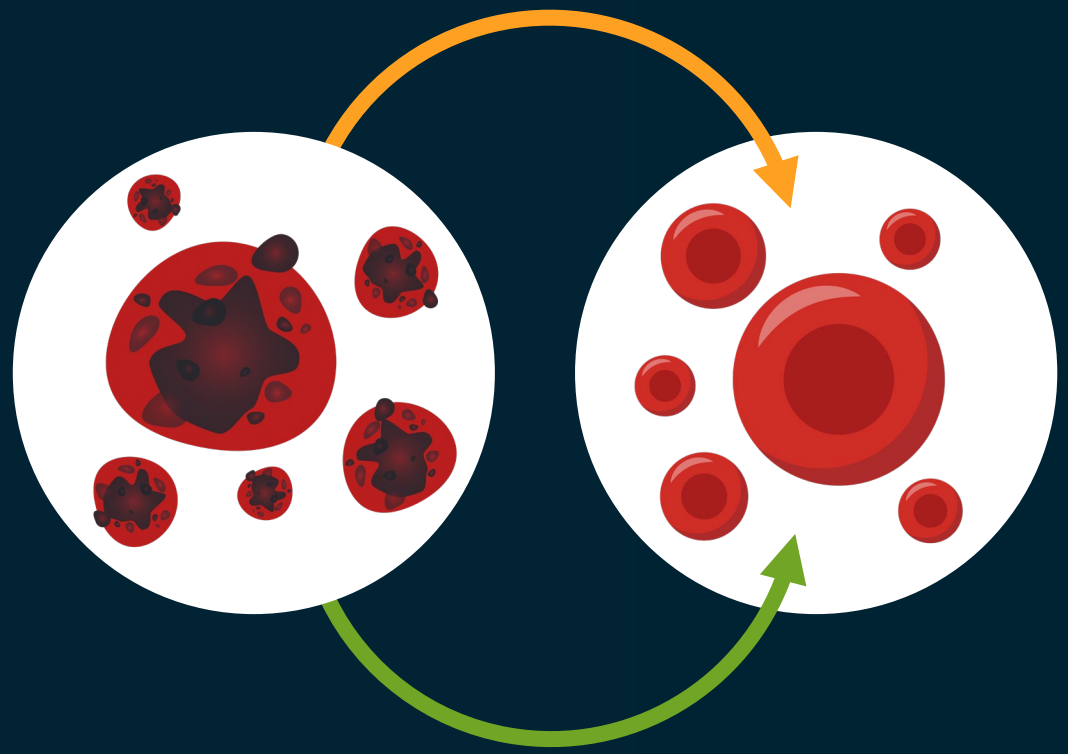
Source: Data presented at ASH 2019; van Beers EJ, et al. Haematologica. 2019;104(2):e51-e53.

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



Increasing ATP enhances RBC energy metabolism, improves overall cell fitness, reduces hemolysis and ameliorates ineffective erythropoiesis



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

Key Inclusion Criteria

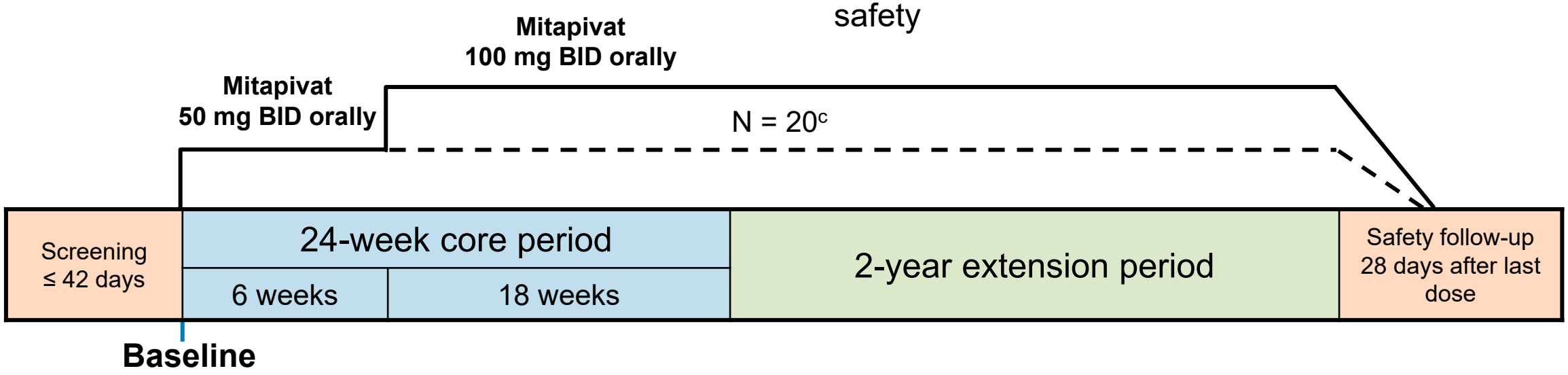
- β-thalassemia ± α-globin gene mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Hb ≤ 10.0 g/dL
- Non–transfusion-dependent[a]

Primary Endpoint[b]

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

Secondary/Exploratory Endpoints

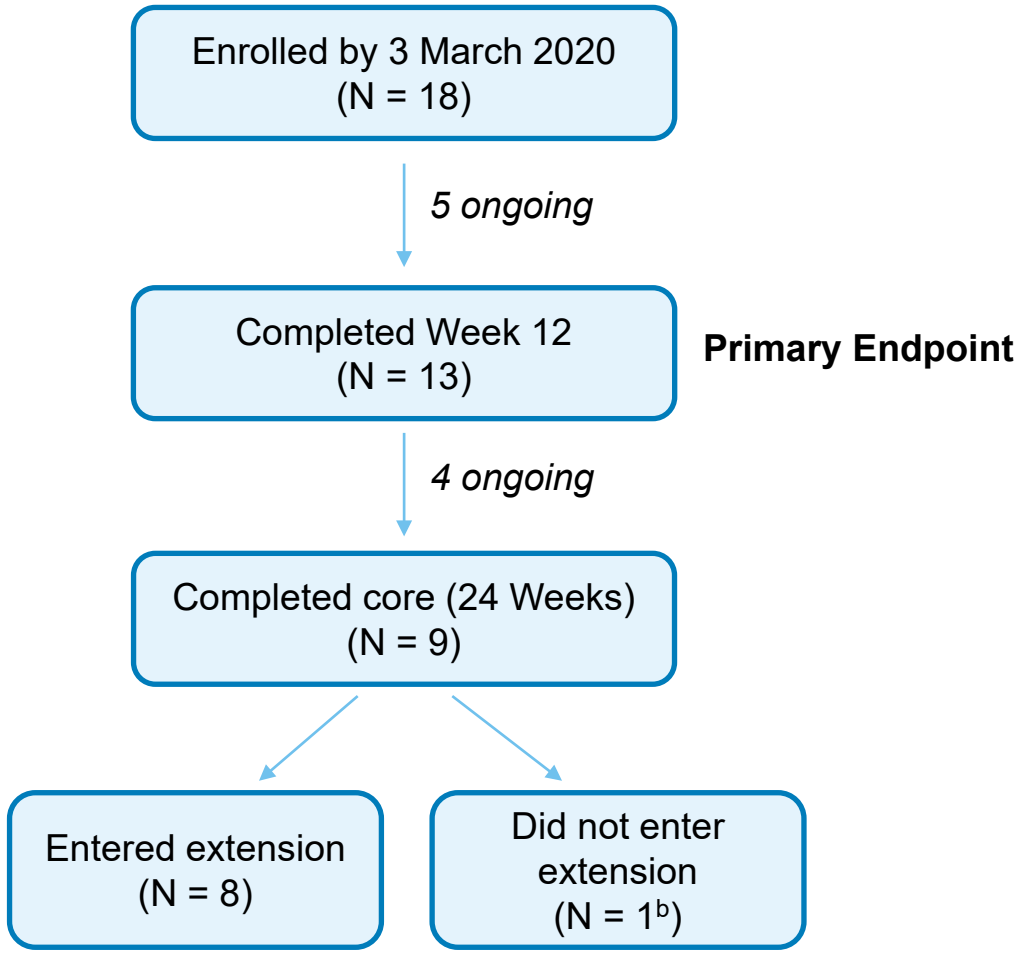
- Sustained Hb response; delayed Hb response; markers of hemolysis; hematopoietic activity; safety



[a]≤ 5 RBC units transfused in the preceding 24 weeks and none in the 8 weeks prior to study drug. [b]With the originally planned sample size of 17 patients enrolled, the study would have 80% power to reject a ≤ 30% response rate at a one-sided 0.05 type 1 error rate. [c]Fully enrolled. BID = twice daily

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)



Hydroxyurea, splenectomy, and prior transfusions were reported in two patients each at baseline
[a]Includes patients who reported more than one category, and one not reported. [b]Investigator decision

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

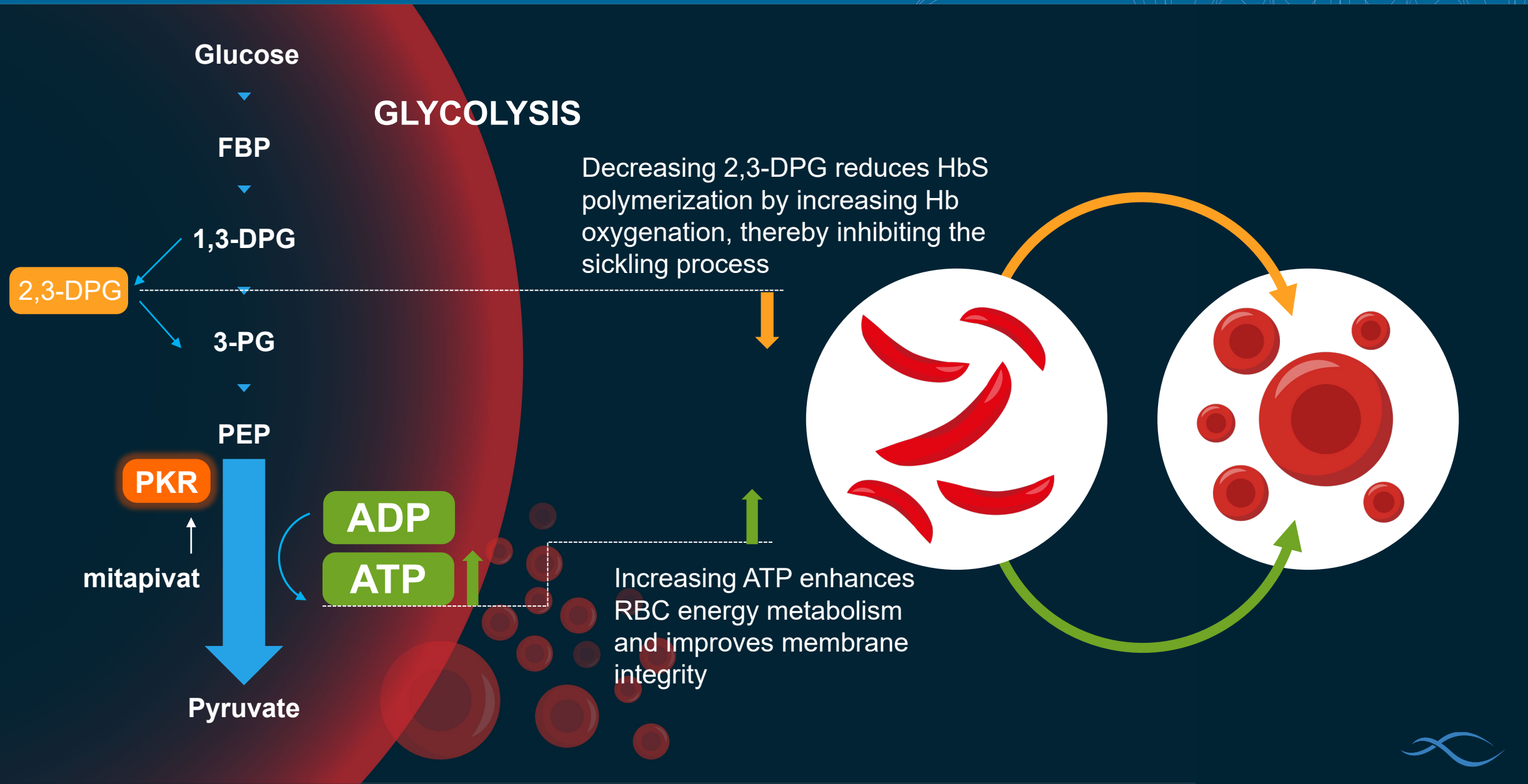
Mitapivat was generally well tolerated; the safety profile was consistent with previous studies

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)

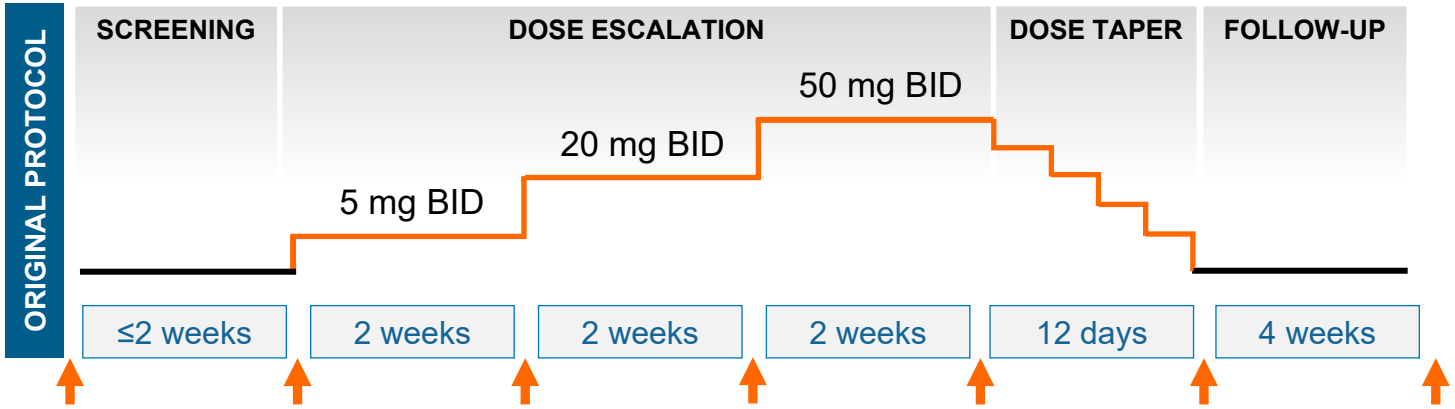
Secondary

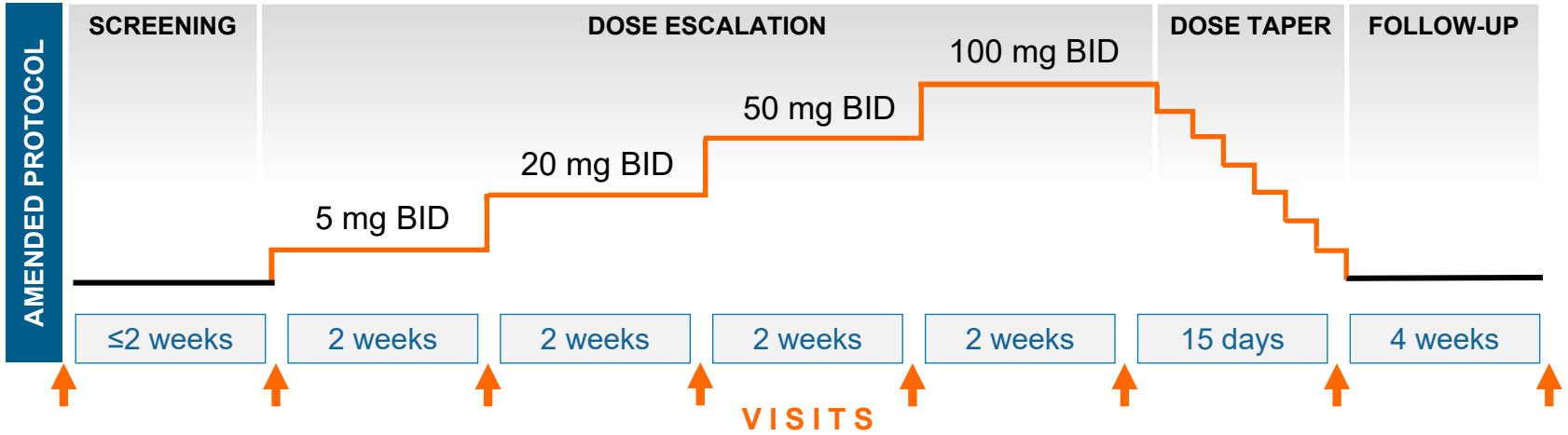
Pharmacokinetics/pharmacodynamics

- 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





CRADA, Cooperative Research and Development Agreement; NHLBI; National Heart, Lung, and Blood Institute; SCD, sickle cell disease; BID, twice daily.

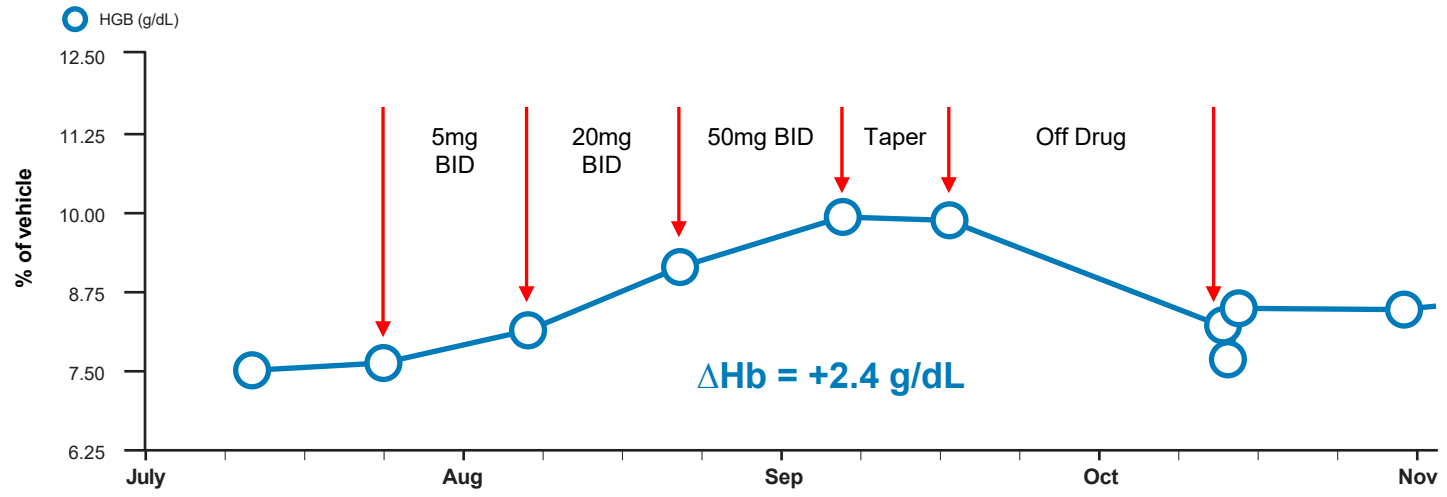
Clinical Proof-of-concept for Mitapivat Established in Sickle Cell Disease

- 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.

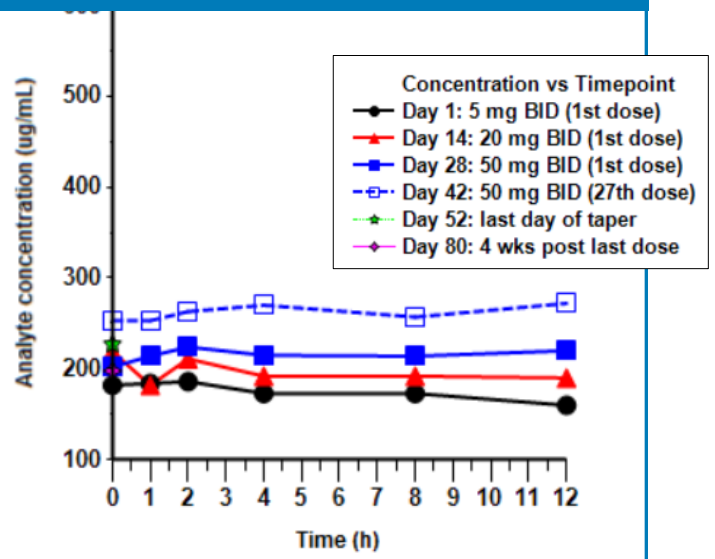
Pivotal plan for mitapivat in sickle cell disease to be initiated in 2021

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

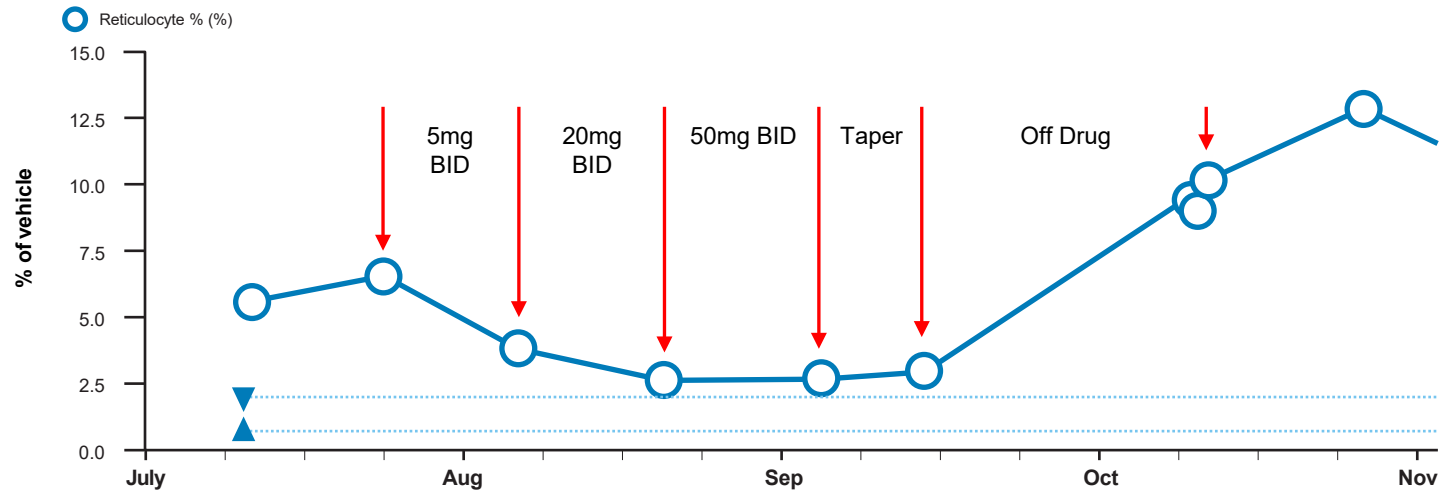
HEMOGLOBIN



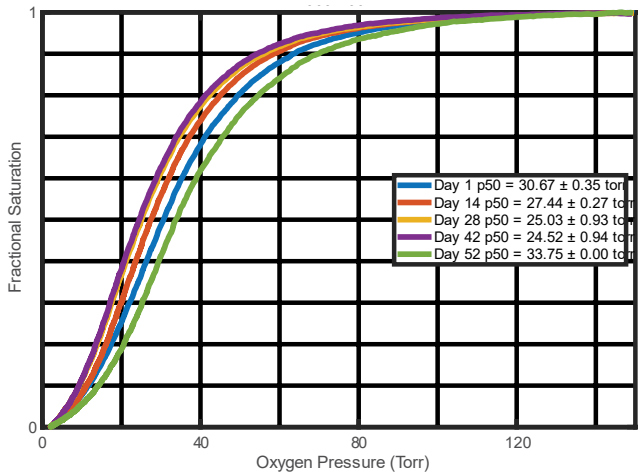
ATP



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

Source: Agios estimates, market research

agios

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

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