IW-3718 Program Update

July 21, 2020

Safe Harbor Statement

This presentation contains forward-looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, including statements our plans to stop enrollment of study subjects into IW-3718-302 and conduct an early assessment of efficacy in that trial, including the independent data monitoring committee's (IDMC) assessment of the trial data, the timing of receipt of outcomes of such assessment, and the nature of the IDMC's recommendation; next steps for the IW-3718 trial following receipt of the IDMC's non-binding recommendation; the scientific integrity, risk profile and power of, and our ability to expeditiously and efficiently advance, the IW-3718 program; the potential use of, and demand for, IW-3718; the anticipated timing of clinical developments and the timing and top-line results of the IW-3718 Phase III trials, including due to the impacts of the COVID-19 pandemic and the recommendation of the IDMC evaluating IW-3718-302; the outcome of our discussions with the FDA regarding potentially including long-term safety data as part of a new drug application submission and whether a long-term safety study is needed to provide additional safety data with an NDA submission; our ability to continue enrolling patients in IW-3718-301; the safety and tolerability of IW-3718; the size of the potential refractory GERD population. These forward-looking statements (except as otherwise noted) speak only as of the date of this presentation, and Ironwood undertakes no obligation to update these forward-looking statements. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include those related to the safety, efficacy and tolerability of IW-3718; the effectiveness and timing of our development efforts; the risk that our clinical programs, studies and development plans may not progress or develop as anticipated, including that studies are delayed or discontinued, or that regulatory submissions are delayed, for any reason, such as safety, tolerability, enrollment, manufacturing, economic or other reasons, including due to the impacts of the COVID-19 pandemic; the risk that findings from our completed nonclinical and clinical studies may not be replicated in the IW-3718-301 and IW-3718-302 studies, our interpretation of the results of those studies are not shared by the FDA or the results of those studies are not consistent; the risk that the therapeutic opportunities IW-3718 are not as we expect; decisions by regulatory and judicial authorities, including the FDA changing its views; the risk that we may never get sufficient patent protection for IW-3718, that patents may not provide adequate protection from competition, or that we are not able to successfully protect such patents; the risk that financial and operating results may differ from our projections; developments in the intellectual property landscape; challenges from and rights of competitors or potential competitors; the risk that our planned investments do not have the anticipated effect on our company revenues; the risk that we are unable to manage our expenses or cash use, or are unable to commercialize our products as expected; and the risks listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended March 31, 2020 and in our subsequent SEC filings. In addition, the COVID-19 pandemic and the associated containment efforts have had a serious adverse impact on the economy, the severity and duration of which are uncertain. Government stabilization efforts will only partially mitigate the consequences. The extent and duration of the impact on our business and operations is highly uncertain. Factors that will influence the impact on our business, operations and financial results include the duration and extent of the pandemic, the extent of imposed or recommended containment and mitigation measures, and the general economic consequences of the pandemic. The pandemic could have a material adverse impact on our business, operations and financial results for an extended period of time.

Today's Agenda

- **Forward-Looking Statements**
  Meredith Kaya, VP Strategy, Investor Relations & Communications
- **Introduction**
  Mark Mallon, Chief Executive Officer
- **IW-3718 Program Update**
  Mike Shetzline, Chief Medical Officer
- **Closing**
  Tom McCourt, President

Ironwood®

IRONWOOD'S VISION & MISSION

Become the Leading U.S. Gastrointestinal Healthcare Company

We are dedicated to **advancing the treatment of GI diseases** and **redefining the standard of care for millions of GI patients**

IW-3718 Phase III Program Updates

- Change to Primary Endpoint
- Early Assessment of IW-3718-302
- Long-Term Safety Data

Ironwood®

IW-3718 Pivotal Phase 3 Program Design

Placebo
+ PPI (BID)

IW-3718
1500 mg + PPI (BID)

8 WEEK TREATMENT PERIOD

Patients

- Two identical, randomized, double-blind, placebo-controlled, multicenter trials of IW-3718
- Designed to enroll adult patients with refractory GERD, as defined as patients who continue to have symptoms despite standard of care (PPI) therapy
- Patients must demonstrate evidence of pathological acid reflux

Endpoints

- Change in weekly heartburn severity – **New Primary** *(prior secondary)*
- Change in weekly regurgitation frequency **– Secondary**
- Overall heartburn response **-** **New Secondary** *(prior primary)*
  - Defined as ≥45% reduction from baseline in heartburn for at least four out of eight weeks
- Proportion of heartburn-free days **– Secondary**

Ironwood®

Primary Endpoint Changed from Responder to Continuous Endpoint

New primary endpoint maintains high powering of Phase III trials

Previous Endpoints

Primary Endpoint

- Overall heartburn responder (≥45%)

Key Secondary Endpoints

- Overall heartburn responder in patients with a baseline Weekly Heartburn Severity Score (WHSS) ≥3[1]
- Percent change from baseline to Week 8 in WHSS
- % change from baseline to Week 8 in Weekly Regurgitation Frequency Score (WRFS)
- Proportion of heartburn-free days during the 8-week treatment period

New Endpoints

Primary Endpoint

- Change from baseline to Week 8 in WHSS

Key Secondary Endpoints

- Change from baseline to Week 8 in WRFS
- Overall heartburn responder (≥45%)
- Proportion of heartburn-free days during the 8-week treatment period

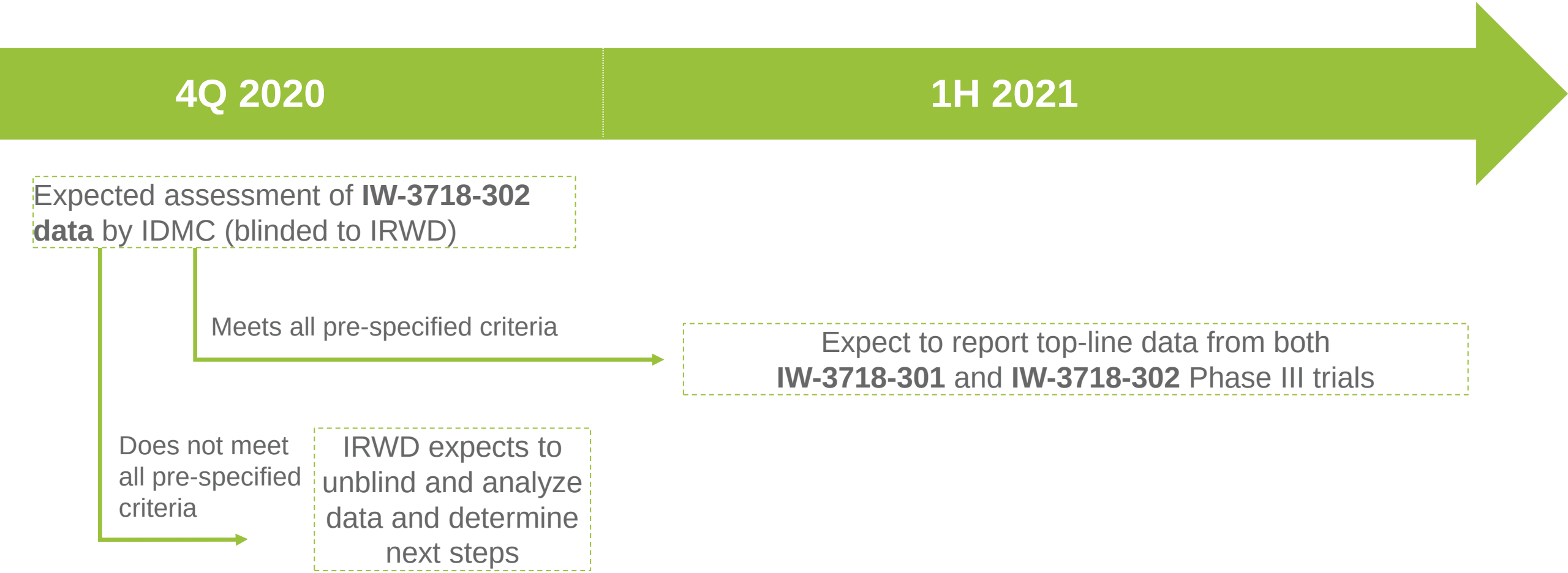
[1]*Overall heartburn responder in patients with baseline WHSS ≥3 moved to exploratory endpoint as aligned to by FDA*

- The **WHSS** for a week is the average of the non-missing Daily Heartburn Severity Scores (DHSS) for that week.
- The **WRFS** for a week is the average of the non-missing Daily Regurgitation Frequency Scores (DRFS) for that week.
- **Regurgitation: "**liquid or food moving upwards toward your throat or mouth" and "an acid or bitter taste in the mouth"

Ironwood®

Opportunity for Evaluation of IW-3718-302; Expect to Report Outcome in 4Q 2020

Opportunity to evaluate IW-3718-302 data given well-powered trial and recent FDA guidance due to COVID-19 pandemic



Ironwood®

Discussing Potential IW-3718 Long-term Safety Data

- FDA requested additional IW-3718 long-term safety data in rGERD patients in connection with an NDA submission
  - Ironwood provided a detailed overview of the existing long-term safety data package for colesevelam – the active ingredient in IW-3718
  - Plan to continue to work closely with FDA to determine whether we will need to conduct a long-term safety study to provide additional safety data as part of an NDA submission
- Colesevelam has a demonstrated safety profile
  - Colesevelam has been used for >20 years for high cholesterol with clinical data evaluating safety for up to 50 weeks
  - IW-3718 has also been shown to be safe in previous clinical trials; no treatment-related serious AEs reported with IW-3718 1500 mg in Phase IIb trial. Most common AE reported overall was constipation.
- Ironwood does not believe this request to be due to any new IW-3718 safety signals
  - Including long-term safety studies is common practice for some therapeutic candidates being developed for long-term, chronic or repeat intermittent use
- The company plans to provide additional details when it has more clarity

IW-3718 Presents Significant Opportunity to Bring Relief for Millions of Adult rGERD Patients (if approved)

High Unmet Need

- ~8-10M U.S. adults suffer from rGERD despite optimized PPI therapy[1,2,3,4]
- A significant portion of patients have esophageal erosions[5]
- 75% of surveyed patients have regurgitation 2+ times per week[,2,4]
- 3x more ER visits than PPI-responsive patients[6]
- Limited number of treatment options available

Compelling Bile Acid Story

- Bile acids play a key role in continued suffering and esophageal injury
- Phase III program supported by positive Phase II data
- 2/3 of rGERD patients exhibit bile reflux[6]
- Potential to reduce heartburn & regurgitation

1st In Class MOA

- IW-3718 is designed to target bile acids & treat rGERD
- Two identical Phase III trials

Established GI Leadership

- GI category leadership positions brand for success
- Expertise to shape market attitudes and behaviors
- Efficient coverage of GI prescribers

1) American Community Survey 2018 (US 18+ population) 2) Lieberman GERD Survey 2010 and 2019 3) My Total Health 2018 4) AHRI GERD Survey 2018 5) Ironwood data; Dickman et al., J Neurogastroenterol Motil 2011 6) Gerson et al., Aliment Pharmacol Ther 2011; Tack et al., Am J Gastro 2004; Ironwood data

Ironwood®