Combination Strategies: Scientific and Regulatory Challenges

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Combination Strategies: Scientific and Regulatory ~~Challenges~~ Opportunities

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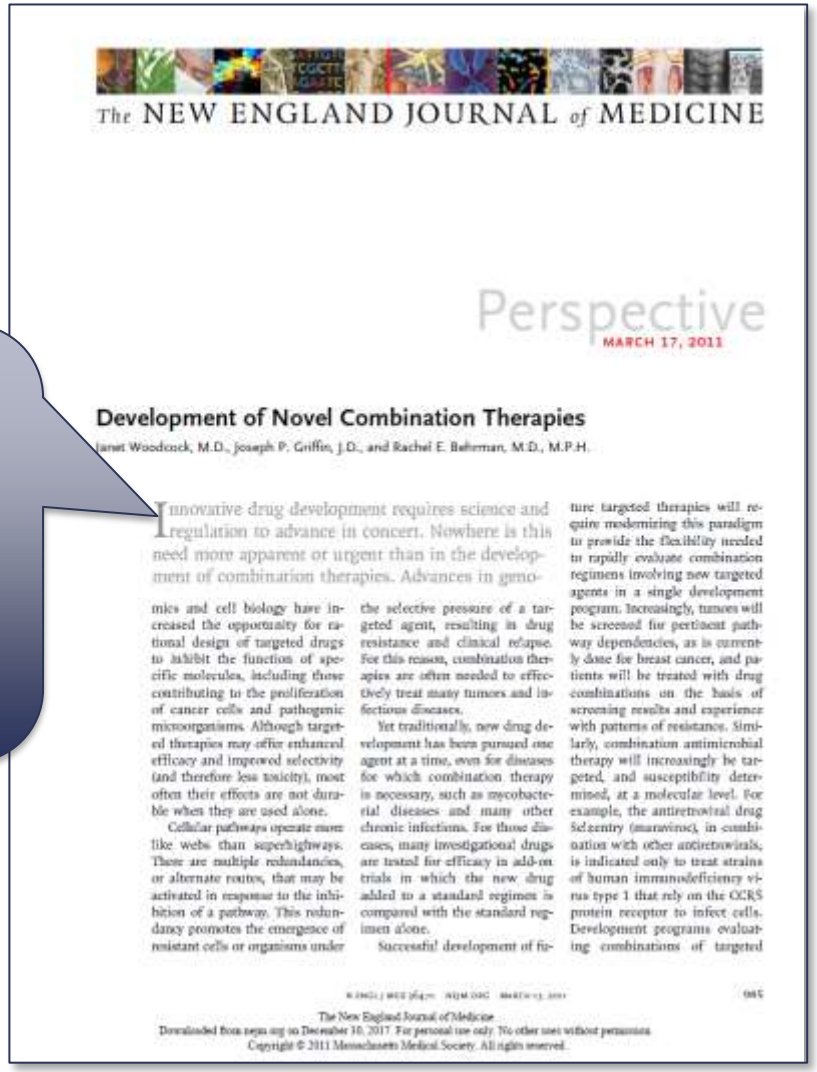
FDA is Open to Innovation to Drive Combination Therapy Development

'Innovative drug development requires science and regulation to advance in concert. Nowhere is this need more apparent or urgent than in the development of combination therapies.'



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MARCH 17, 2011

Development of Novel Combination Therapies

Janet Woodcock, M.D., Joseph P. Griffin, J.D., and Rachel E. Behrman, M.D., M.P.H.

Innovative drug development requires science and regulation to advance in concert. Nowhere is this need more apparent or urgent than in the development of combination therapies. Advances in genomics and cell biology have increased the opportunity for rational design of targeted drugs to inhibit the function of specific molecules, including those contributing to the proliferation of cancer cells and pathogenic microorganisms. Although targeted therapies may offer enhanced efficacy and improved selectivity (and therefore less toxicity), most often their effects are not durable when they are used alone.

Cellular pathways operate more like webs than superhighways. There are multiple redundancies, or alternate routes, that may be activated in response to the inhibition of a pathway. This redundancy promotes the emergence of resistant cells or organisms under the selective pressure of a targeted agent, resulting in drug resistance and clinical relapse. For this reason, combination therapies are often needed to effectively treat many tumors and infectious diseases.

Yet traditionally, new drug development has been pursued one agent at a time, even for diseases for which combination therapy is necessary, such as mycobacterial diseases and many other chronic infections. For those diseases, many investigational drugs are tested for efficacy in add-on trials in which the new drug added to a standard regimen is compared with the standard regimen alone.

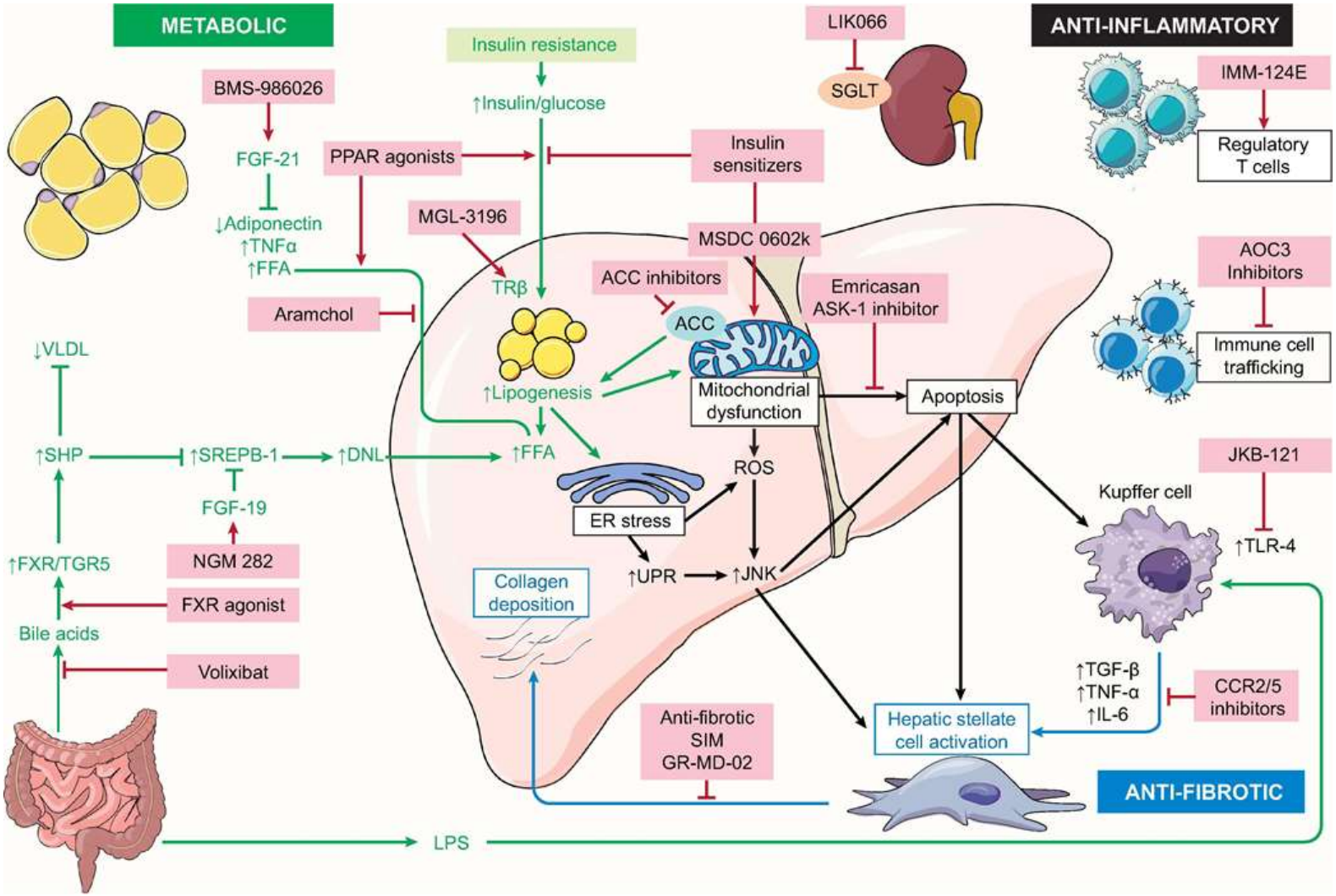
Successful development of future targeted therapies will require modernizing this paradigm to provide the flexibility needed to rapidly evaluate combination regimens involving new targeted agents in a single development program. Increasingly, tumors will be screened for pertinent pathway dependencies, as is currently done for breast cancer, and patients will be treated with drug combinations on the basis of screening results and experience with patterns of resistance. Similarly, combination antimicrobial therapy will increasingly be targeted, and susceptibility determined, at a molecular level. For example, the antiretroviral drug Selzentry (maraviroc), in combination with other antiretrovirals, is indicated only to treat strains of human immunodeficiency virus type 1 that rely on the CCR5 protein receptor to infect cells. Development programs evaluating combinations of targeted

Woodcock J., et al. N Engl J Med 364;11

Presentation Outline

- Why Combination Therapy?
- Safety and Efficacy Considerations
  - Learning from Other Disease Areas
  - Practical Issues
- Regulatory View

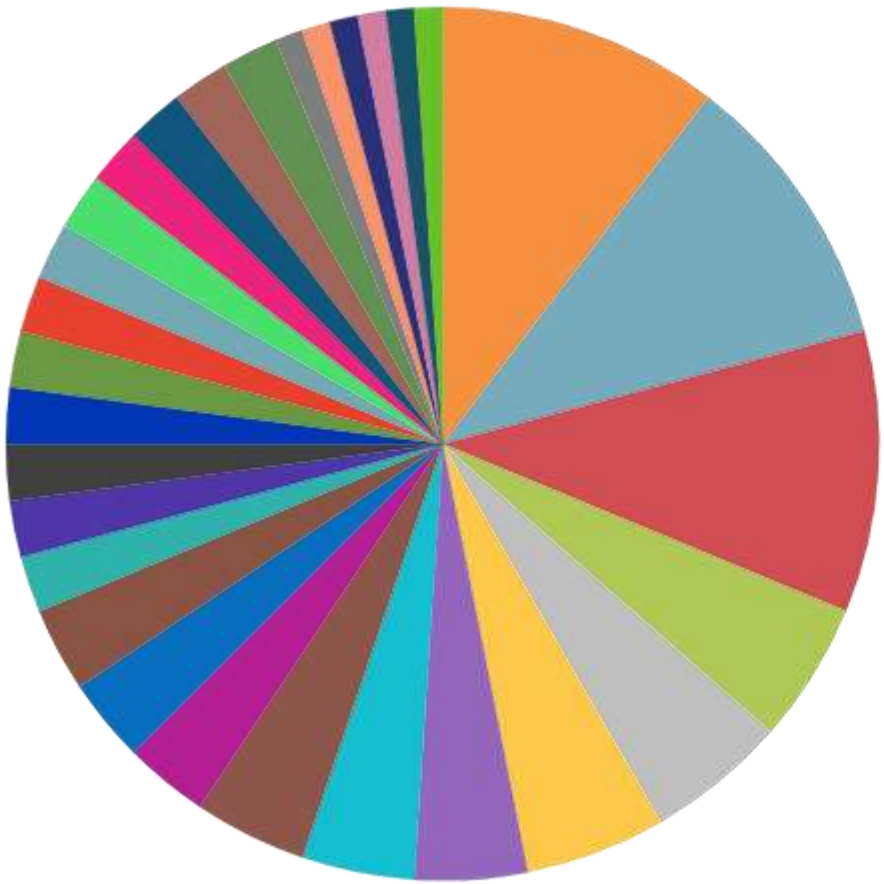
Reason #1: Multiple Complex Disease Pathways



Konerman MA et al. Pharmacotherapy for NASH: Current and emerging. J Hepatol (2017), https://doi.org/10.1016/j.jhep.2017.10.015

Reason #2: Very Deep Pipeline of Assets

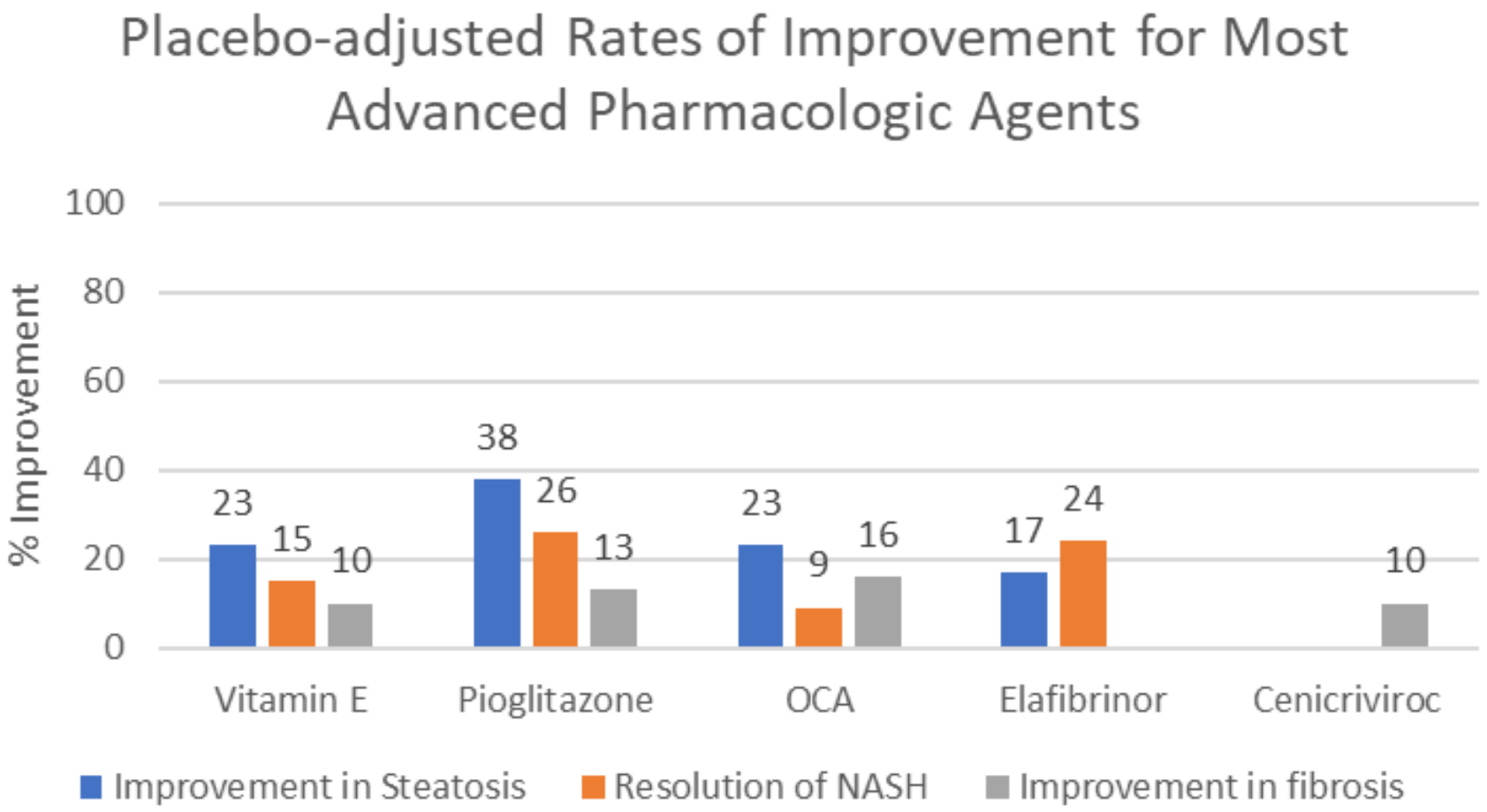
~96 Compounds in Development for NASH



Farnesoid X receptor agonist	10
Glucagon-like peptide 1 agonist	10
Insulin sensitizer	10
CCR2 chemokine antagonist	5
Glucagon receptor agonist	5
PPAR gamma agonist	5
FGF-21 ligand	4
PPAR alpha agonist	4
PPAR delta agonist	4
Ileal sodium bile acid cotransporter inhibitor	3
MEKK-5 protein kinase inhibitor	3
NACHT LRR PYD domain protein 3 inhibitor	3
Acetyl CoA carboxylase inhibitor	2
Amylin receptor agonist	2
Angiotensin II AT-1 receptor antagonist	2
Calcitonin agonist	2
Cannabinoid CB1 receptor antagonist	2
Cathepsin B inhibitor	2
CCR5 chemokine antagonist	2
Extracellular matrix protein modulator	2
Galectin-3 inhibitor	2
PDE 5 inhibitor	2
Sodium glucose transporter-2 inhibitor	2
Thyroid hormone receptor beta agonist	2
5-Lipoxygenase inhibitor	1
ACE inhibitor	1
Adenosine A3 receptor agonist	1
Adiponectin receptor agonist	1
Aldehyde dehydrogenase 2 stimulator	1
Aldosterone antagonist	1

Source: Competitive Intelligence

Reason #3: Single Agents Produce Meaningful but Modest Improvements



Adapted from: Konerman MA et al. Pharmacotherapy for NASH: Current and emerging. J Hepatol (2017), https://doi.org/10.1016/j.jhep.2017.10.015

Portfolio Versus Single Asset Approach

Portfolio

Pro

- Facilitates combination development at will
- Maintain full control
- Can move forward quickly
- Open regulatory discussions

Con

- Requires significant capital
- 'Forces' combination to fit own portfolio
  - Each asset may not be best-in-class
- Strategy based on what you have versus what you can access externally

Single Asset

Pro

- Total focus on one asset
- Can evaluate all external options and partner with best molecules
  - 'friend-to-all' strategy
- Can lead to acquisition (+/-)

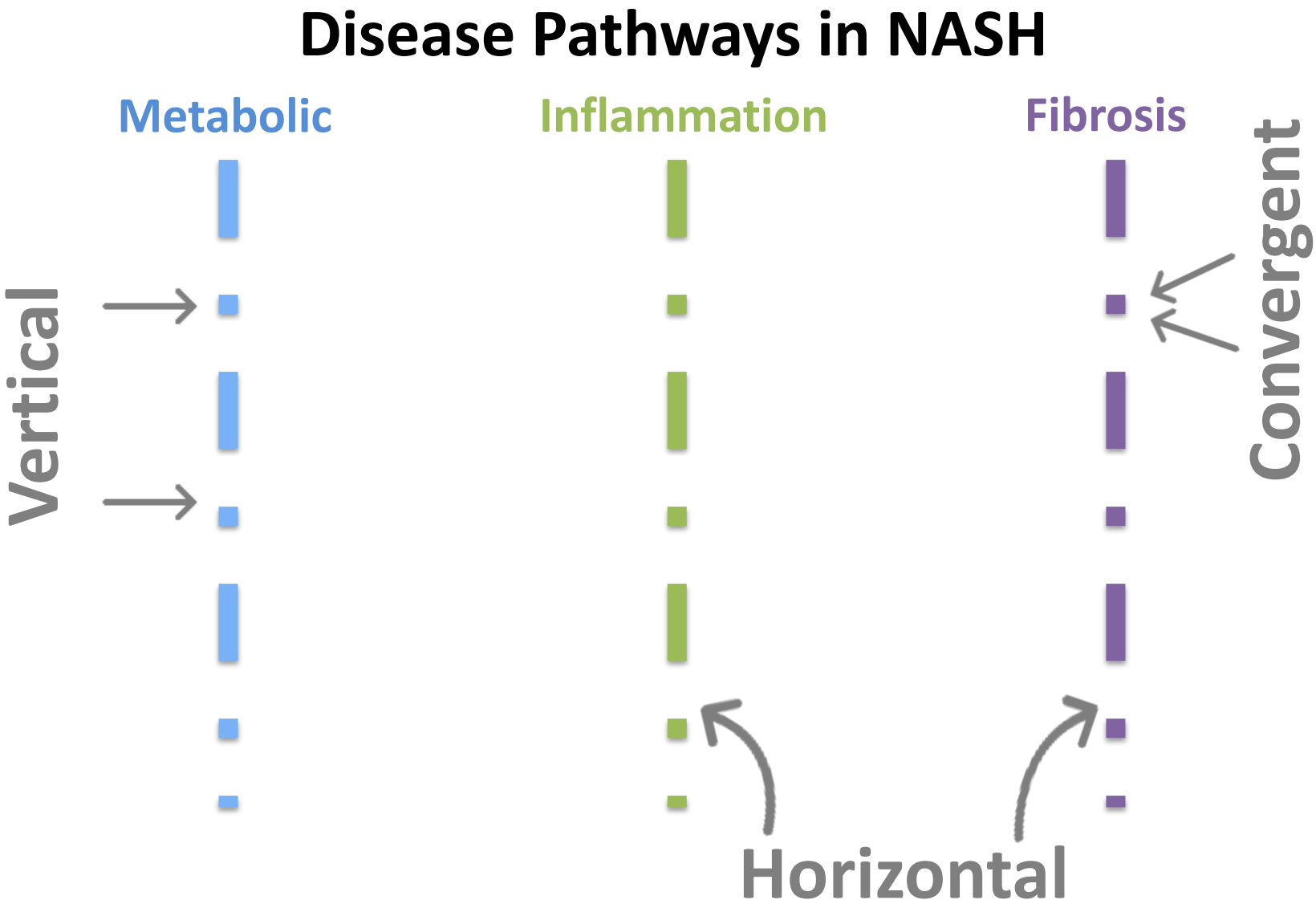
Con

- Working with external partners can be time consuming
- May not maintain complete control over combination program
- Multiple parties involved in regulatory discussions

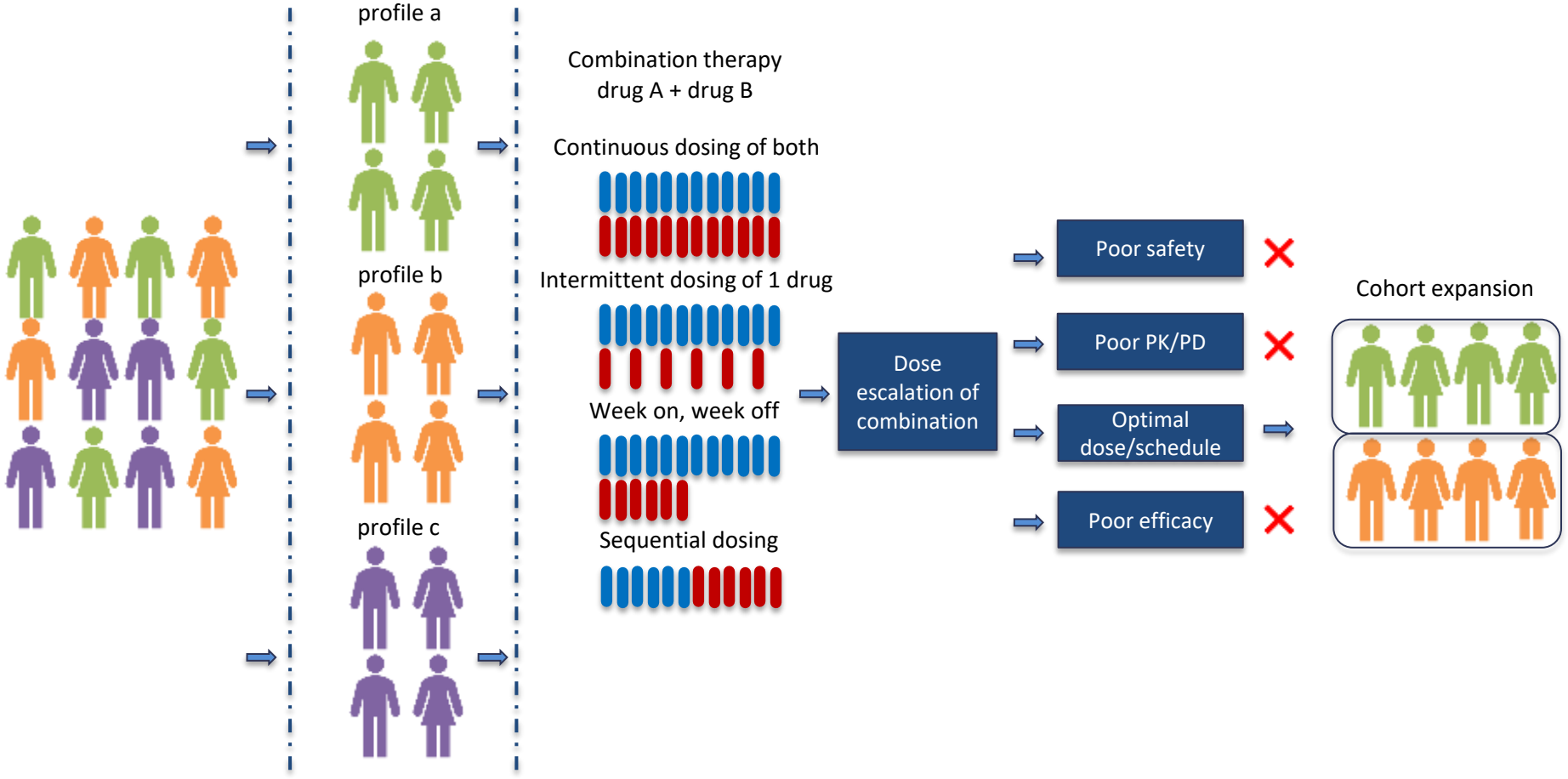
Combination Development : ‘Drug-centric versus Strategy-centric”

- We are good at developing single agents
- Majority of approved combinations based upon 1 or more approved agents
- Goal is to achieve more efficacy than possible with individual agents with good safety and tolerability
  - Use rationale approach to select components
- Leverage learnings from development in other diseases

Target Selection Strategies for Combination Therapy Components



Adaptive Approach to Selecting Best Combination Regimen from Oncology Applied to NASH



Patients matched to treatment strategy based upon disease profile

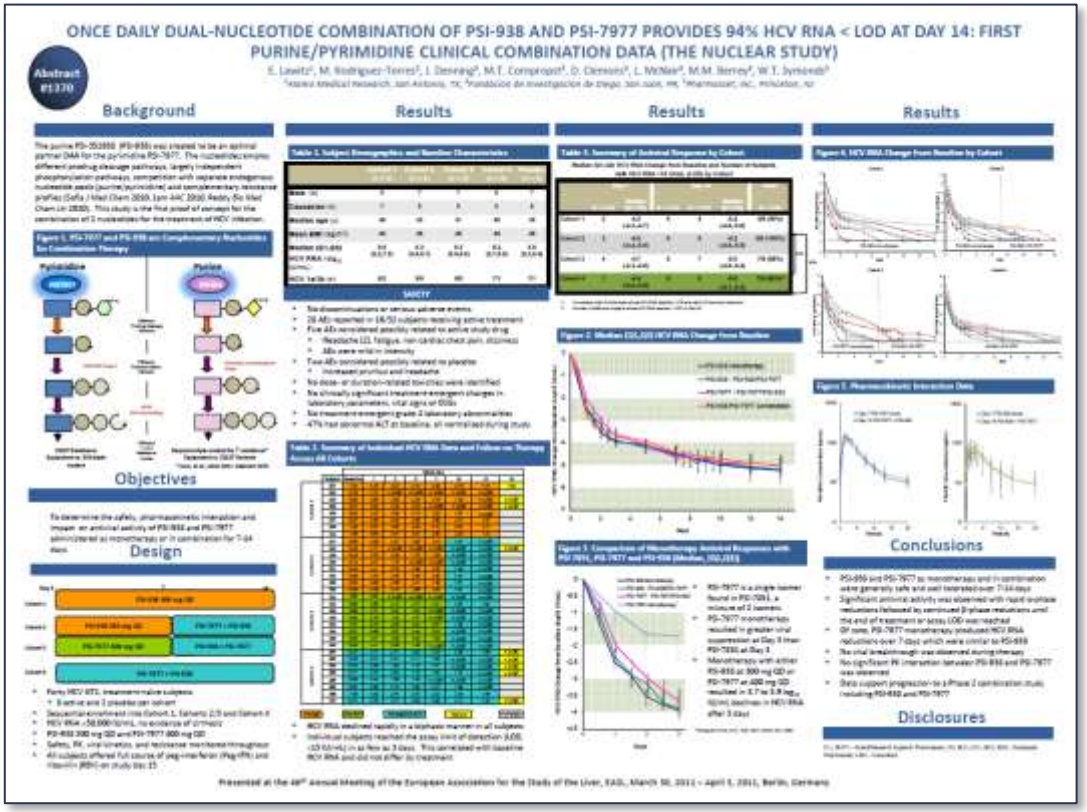
Adapted from: Day and Siu Genome Medicine (2016) 8:115

Safety Considerations for Combination Development

- Drug-drug interactions
  - Preclinical (CYP's, transporters, elimination routes) and clinical
- Overlap in preclinical toxicity profiles
- Physicochemical properties
- Route of administration, dose, schedule
- Extent of human safety data for each agent

How Much Safety Data Is Needed to Support Combination Studies?

- PSI-938
  - SAD data up to 1600 mg
  - MAD data up to 300 mg QD for 7 days with ↓ HCV RNA and ↓ ALT
- PSI-7977
  - SAD and MAD data
  - 28-Day study in combo with PEG/RBV


ONCE DAILY DUAL-NUCLEOTIDE COMBINATION OF PSI-938 AND PSI-7977 PROVIDES 94% HCV RNA < LOD AT DAY 14: FIRST PURINE/PYRIMIDINE CLINICAL COMBINATION DATA (THE NUCLEAR STUDY)

Abstract #1370

Background

Objectives

Design

Results

Results

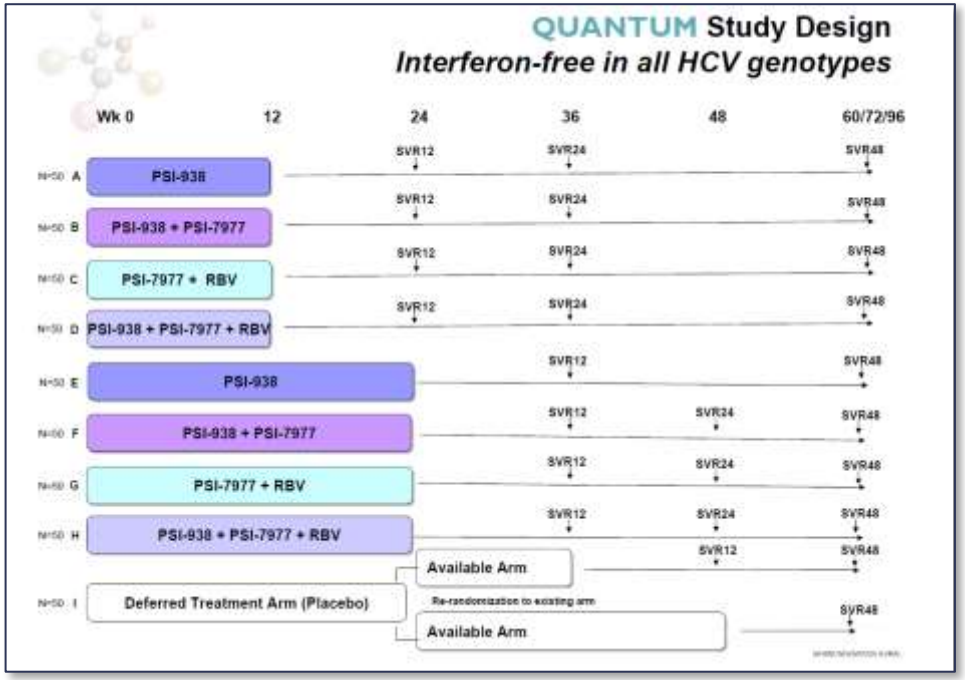
Results

Conclusions

Disclosures

How Much Safety Data Is Needed to Support Combination Studies? *NUCLEAR to QUANTUM*

- PSI-938
  - SAD data up to 1600 mg
  - MAD data up to 300 mg QD for 7 days with ↓ HCV RNA and ↓ ALT
  - **NUCLEAR data up to 14 days**
- PSI-7977
  - SAD and MAD data
  - 28-Day study in combo with PEG/RBV
  - **12-Week data from multiple Phase 2 studies with PEG/RBV**



How Much Safety Data Is Needed to Support Combination Studies?

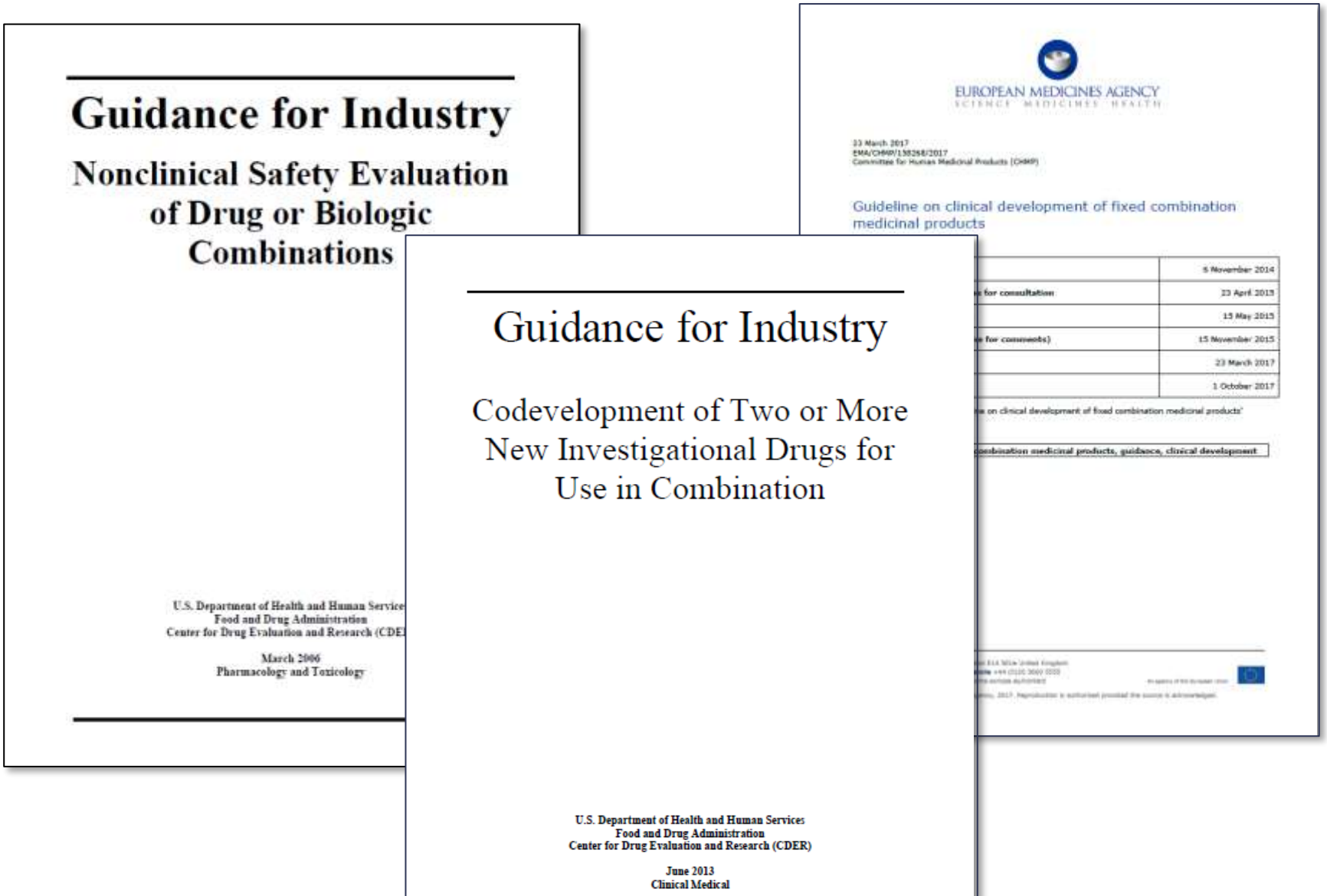
PRINCETON, N.J., Dec. 16, 2011 /PRNewswire/ --

Pharmasset, Inc. (Nasdaq: VRUS) announced today that the company will amend the design of the QUANTUM Phase 2b trial of the guanine nucleotide analog PSI-938 and discontinue all treatment arms with a regimen containing PSI-938. There are 235 individuals with hepatitis C virus (HCV) in the study who are receiving treatment with PSI-938 alone or in combination with PSI-7977 or PSI-7977 and ribavirin. During routine safety monitoring, the company detected laboratory abnormalities associated with liver function in subjects receiving PSI-938 300 mg once daily. These laboratory abnormalities have not been observed in patients receiving PSI-7977 and ribavirin in the QUANTUM study or in other trials evaluating PSI-7977. Both the 12 and 24-week PSI-7977 and ribavirin arms will continue unchanged, data from which will support NEUTRINO, an interferon free, 12-week Phase 3 study of PSI-7977 and ribavirin in patients with HCV genotype 1 (GT-1).

Drug and Biologic Combinations May Involve…

- Two or more previously marketed drugs or biologics
- One or more new molecular entities and one or more previously marketed drugs or biologics
- Two or more New Investigational Drugs
  - Subject of ‘Co-development’ FDA Guidance Document

A number of Regulatory Guidance Documents are Available



General Requirements for Co-Developed Products

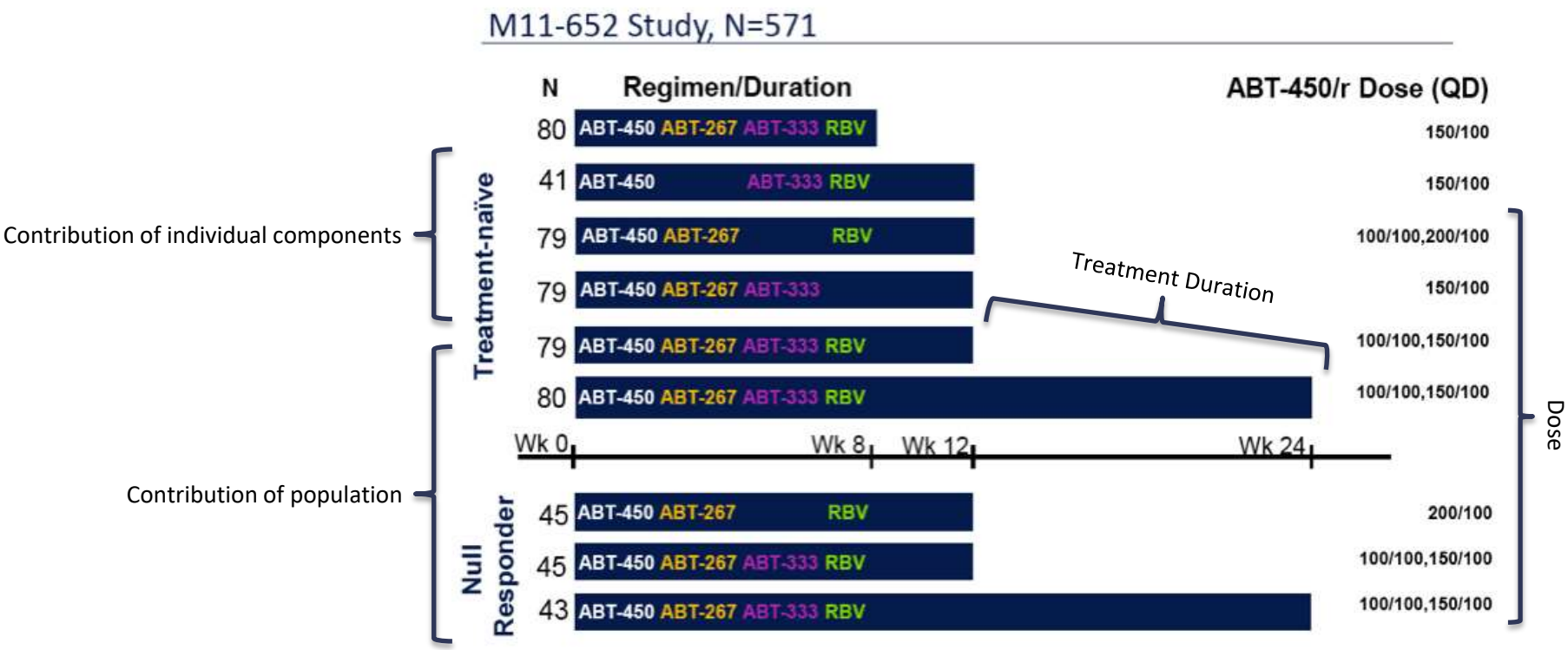
- Rationale supporting combination and doses
- Animal toxicology data (single +/- combination tox?)
- Drug-drug interaction data, if needed
- Demonstrate benefit of each investigational agent
- Safety data:
  - 2 NME's: individual programs support safety
  - 1 marketed + 1 NME: safety data for approved drug can support along with individual data for NME

Viekira Pak: First Time Three NME's filed in a Single Regulatory Application

- Approval Status: FDA approval on December 19, 2014
- Indication: Genotype 1 chronic HCV infection, including compensated cirrhosis
- Key data: 14-arm Phase 2 study showing individual contribution of each agent in the combination
- Nonclinical: Toxicology studies performed with individual compounds, no combination toxicology required

- Component drugs & Mechanism
  - Ombitasvir (ABT-267): NS5A inhibitor
  (2nd NS5A inhibitor filed)
  - Paritaprevir (ABT-450): NS3/4A serine protease inhibitor
  (4th PI filed)
  - Ritonavir: HIV protease inhibitor used as pharmacologic booster
  (previously approved)
  - Dasabuvir (ABT-333): Non-nucleoside NS5B polymerase inhibitor
  (1st NNI filed)

Key Study: Phase 2 (Aviator) Trial Designed to Demonstrate Contribution of 3 Different Drugs



Learnings from Past Combination Programs

- Think through the complete development plan
  - Plan for and complete pre-requisites
  - Generate preclinical data where possible to support
  - Think through and plan how you will select components, doses/schedules, endpoints based on MOA's involved, etc.
- Share full strategy and plan with regulators early
  - Help them help you by being fully transparent
- Don't submit a complex combination protocol without context

Combination Development is Happening

- Develop a solid scientific rationale
- Think through the development plan and take care of pre-requisites ahead of time
- Learn from other therapy areas where innovative trial designs are being developed
- Be mindful of safety – don't let one drug take down a portfolio
- Regulators are receptive and open to discussion
  - Read available guidance documents
  - Study precedent programs
  - Talk with them early and often

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How to Work With FDA

- Take advantage of all opportunities to learn from and interact with FDA
- Be honest and transparent
- Treat FDA staff with respect and courtesy
- Recognize the knowledge and expertise of FDA staff
- Listen very carefully
- Give full consideration to FDA comments
- Remain calm
- Avoid becoming angry and threatening
- Ask follow up questions
- If there is a disagreement, follow the chain of command to try and resolve
- Follow established procedures and timelines for meetings and dispute resolution; avoid unnecessary requests for special treatment