THE FORUM FOR COLLABORATIVE RESEARCH

LIVER FORUM 8

Summary of Proceedings

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THE FORUM For Collaborative Research℠

Berkeley School of Public Health

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SESSION I: PROJECT & REGULATORY UPDATES

Introduction and Welcome

Presenter: Katherine Greene, Forum for Collaborative Research

Slides: https://goo.gl/byymmH

Overview of the Liver Forum:

- What:
  - A platform that allows for ongoing multi-stakeholder dialogue specifically about regulatory issues and clinical trials related to NAFLD/NASH
  - Identify barriers and gaps, prioritize research, and identify solutions to accelerate therapeutic development
  - "Ongoing" is key- the in-person meetings are only a part of what the Liver Forum does, and the real meat of the work occurs throughout the rest of the year.
- Who:
  - Multistakeholder initiative comprised of regulators, professional societies, patient representatives, academic and clinical researchers, industry organizations, research consortia, and non-profits
  - Participants are scientific experts
  - Individuals and organizations participating have a commitment to advancing the field
  - Not the place for commercial or marketing activity, investors, or journalists
  - Participation is by invitation (from Forum staff)
- How:
  - Provide a neutral and independent space that allows for open discussions across the various stakeholder groups
  - Focus is to develop consensus where feasible, reduce duplication of efforts, and increase collaboration across stakeholder groups
  - The Liver Forum is a process, and the working groups are on-going throughout the year
  - Participants in the Liver Forum are expected to actively engage and contribute to discussions and consensus building processes
- Why:
  - NAFLD and NASH is an area of unmet medical need
  - All stakeholder groups will need to work together in order to get therapeutics developed and approved, to be able to provide treatment options for patients
- Other Guidelines:
  - "What's said in the room stays in the room"
    - Comments made and questions asked during the course of the meeting are not for attribution.
    - Everyone is participating as an individual expert
      - Comments by individuals from regulatory agencies do not constitute the official view of that regulatory agency
    - Allows for more open discussions and more open questions
- Steering Committee Updates:
  - Dr. Naga Chalasani has been appointed by AASLD, replacing Dr. Stephen Harrison
  - Dr. Annalisa Berzigotti who has been appointed by EASL, replacing Dr. Laurent Castera, and Dr. Tom Hemming-Karlson

Current Activities

- Recent Accomplishments
  - Baseline Parameters manuscript has been published

        - Patel YA, Imperial JC, Muir A. Baseline parameters in clinical trials for nonalcoholic steatohepatitis: Recommendations from the liver forum. Gastroenterology 2017, 153(3):621-625.e7. https://doi.org/10.1053/j.gastro.2017.07.024
    - Case Definitions manuscript has been published
        - Siddiqui MS, Harrison S, Abdelmalek M, Anstee Q, Bedossa P, Castera L, et al. On behalf of the Liver Forum Case Definitions Working Group, Case definitions for inclusion and analysis of endpoints in clinical trials for NASH through the lens of regulatory science. Hepatology 2018, 67(5):2001-2012. http://doi.org/10.1002/hep.29607
- Working Groups:
    - Case Definitions
        - The second manuscript on defining improvement in NAFLD for treatment trial endpoints is nearing completion and will then undergo a final FDA review before it is submitted for publication
    - Pediatric Issues
        - The first manuscript is completed and undergoing final FDA review before submission for publication
    - Standard of Care: Lifestyle
        - Developing 1st draft of recommendations for standardization of lifestyle management in clinical trials
    - Standard of Care: Comorbidities
        - The "Standard of Care" working group was recently split into two workstreams, creating the Comorbidity Management working group. The group is in the first stages of developing an outline for recommendations.
    - NASH Cirrhosis
        - The newest working group that is meeting for the first time during the breakout sessions.
- Other Activities
    - Core Outcomes in NASH Project
        - The Center for Medical Technology Policy has invited the Liver Forum to partner on this initiative, along with the Obesity Action Coalition, to develop multi-stakeholder consensus on outcomes to be used in NASH clinical trials
    - NASH Biomarker Workshop
        - The Liver Forum is co-organizing this workshop again this year along with Expert Medical Events.
        - The workshop will take place May 18-19, in Washington DC
    - Paris NASH Meeting
        - Dr. Veronica Miller from the Liver Forum is co-organizing the Paris NASH Meeting this year along with Drs. Lawrence Serfaty and Dr. Arun Sanyal
        - July 5-6, Paris France

Champion of Collaboration Award

Presenter: Veronica Miller, Forum for Collaborative Research

Awardee: Cheronda Cherry-France

Slides: **https://goo.gl/khNrRT**

Award Presentation:

- The 2nd "Champion of Collaboration" Award presented to Cheronda Cherry-France for Outstanding Service and Commitment in the Field of Liver Disease

- Cheronda Cherry-France is a Commissioned Corps officer with the rank of Commander (CDR) within the United States Public Health Service (USPHS).
- CDR Cherry-France has an extensive background in nursing, leadership, and research management and is currently serving dual roles as co-Chief Project Manager and one of five Senior Regulatory Health Project Managers (SRPM) assigned to the Division of Gastroenterology and Inborn Errors Products (DGIEP).
- She currently supports DGIEP with managing over 70 employees to include medical officers, regulatory project managers, scientist, program specialist, and pharmacology reviewers. CDR Cherry-France co-manages over 100 liver agents assigned to the Division.
- She is dedicated to protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

Core Outcomes in NASH Project

Presenter: Donna Messner, Center for Medical Technology Policy

Slides: https://goo.gl/sN4MGh

Organizational Overview

- The Center for Medical Technology Policy (CMTP) is an independent, non-profit located in Baltimore Maryland, whose mission is to make healthcare more effective and affordable by improving quality, relevance, and efficiency of clinical research.
- A core commitment is to engage all relevant stakeholders to improve clinical research design and research infrastructure, and promote evidence-based policy.
- The Green Park Collaborative (GPC) is a major initiative of CMTP which focuses on evidence-based policy.
    - Use multi-stakeholder approach to develop shared understanding of evidence needs of 'post-regulatory' decision-makers.
        - Payers, health technology assessors, patients, and health systems.
        - Individuals/groups who need to make decisions based on the information that came out of the regulatory process.
    - Create greater transparency for innovators to be able to better anticipate what is going to be needed in terms of clinical evidence to demonstrate effectiveness and value.
    - Focus is on "reimbursement science".
- The Core Outcomes in NASH project will be a partnership between CMTP/GPC, the Liver Forum, and the Obesity Action Coalition.

Reimbursement Science

- Regulatory Science focuses on developing new tools, standards, and approaches to assess safety, efficacy, quality, and performance of regulated products.
- Reimbursement Science focuses on developing new tools, standards, and approaches to assess the comparative effectiveness and value for covered products and the decisions of public and private payers.
    - CMTP has been working in this area and developing relationships with payers and HTA groups for over a decade.
- Value: "health outcomes achieved per dollar spent"
    - $\frac{Health\ Outcomes}{Dollars}$
        - There are many different outcomes which each have different measures that can be used. How to make that decision?
        - Need to make sure that the correct outcomes have been identified and incorporated into this formula.

        - Different decision makers have different perspectives on what drives value.
- Core Outcome Sets
    - A minimum set of outcomes that a multi-stakeholder group has agreed should be collected in all clinical trials for a given condition.
    - Doesn't limit the outcomes that you can choose to use in your clinical trials.
    - The idea is to define through a structured consensus process, a core set of outcomes that everybody agrees is going to be relevant to decision-makers and should be measured and reported in clinical trials.

Project Rationale and Process

- This is an opportune time to begin this project
    - Many new products are currently in development
    - There is a potentially large patient population
    - Important public health issues at stake
    - Payers and HTAs are aware and paying attention to the developments in this area and there is uncertainty about how they will evaluate new treatments for NASH when they are approved by regulators.
        - Better to have the conversation early so there is still time to make adjustments to clinical plans based on what is learned.
- Project Process
    - A multi-stakeholder group of about 50 participants is assembled
        - Regulatory, methods and clinical experts, industry, patients/ patient advocates, payer and HTA groups, and health systems
    - An advisory group develops an initial set of outcomes and definitions
    - That list will be used in a structure consensus process
    - All stakeholder groups have the opportunity to hear from other groups what outcomes are important.
- Previous Example
    - CoreHEM – late phase gene therapy trials in hemophilia
        - Completed project in 9 months to be able to quickly inform the trials of the participating companies
        - All companies were committed to using the core set, and some have amended previously submitted protocols to reflect the consensus outcomes.
        - The project had 12 payer/HTA groups that participated
            - Working to develop consensus statement in support of companies utilizing the core outcome set.
    - Can be accomplished, done in a timely fashion, and have a major impact.

U.S. Food and Drug Administration Regulatory Update

Presenter: Lara Dimick-Santos, U.S. Food and Drug Administration

Slides: https://goo.gl/ez7eKA

Surrogate Endpoints

- All accepted surrogate endpoints in NASH are based on histopathology and not much data.
    - To promote drug development, endpoints of one-point improvement in liver fibrosis and resolution of steatohepatitis are based on theory.
    - Since the diagnostic criteria for NASH is histology, it made sense to use a change in the histopathology for a surrogate
        - With understanding that "feels, functions, and survives" endpoints that could validate these surrogates would be looked at down the road.
- Histologic progression to cirrhosis

    - Is accepted as a clinical benefit endpoint
    - Large amount of data in the literature supporting that getting cirrhosis is bad, and leads to poor health outcomes including death.
    - Data supports that slowing the 'rate of' or 'time to' progression to cirrhosis predicts a decrease in adverse clinical outcomes.
- Histologic resolution of cirrhosis
    - Not enough data for the histopathology
    - Reduction in fibrosis has not been shown to predict clinical benefit, or to improve liver function.
    - Some clinical trials are using endpoints of one-point improvement in cirrhotic populations.
        - There is some data in hepatitis regarding patients improving their fibrosis score, though not all data will be translatable to NASH
        - Patients might improve with improvement of fibrosis but still have active underlying disease, and there remain uncertainty of how that relates to long-term treatment and if the endpoint can predict outcomes.
    - Originally the one-point improvement of fibrosis was considered for non-cirrhotic populations.
        - In cirrhosis population, some patients will have some well-established biomarkers that could be measured and should be evaluated to support that a one-point improvement in fibrosis results in improvement in synthetic function of the liver.
            - For example, bilirubin, platelets, INR, albumin

Discussion

C: CHMP has in at least one case accepted the reversal of cirrhosis as an acceptable surrogate endpoint; however, the data are quite scarce. It raises the question of whether a surrogate is needed in cirrhotic populations, or if the better option would be to go for hard outcomes.

- Within cirrhosis there is a lot of subcategorization, and a patient with early stage 4 cirrhosis may take many years to progress to hard outcomes.
- Hard outcomes are transplant, death (all-cause mortality), and decompensation events.
    - The FDA accepts two other outcomes: progression to cirrhosis, and change in MELD score from <12 to ≥15 (substitute for listing for transplant).
        - The MELD endpoint is used in compensated cirrhotic populations with a low MELD score.
        - The progression to cirrhosis endpoint is not relevant to a cirrhotic population.
            - Trials might potentially last longer
                - Length of trial is uncertain – in a cirrhotic-only population, there is a high increased disk of development of the hard outcomes. It is unknown if that would increase length, or actually decrease length.

C: Cirrhosis is a continuous disease, and it would need to be taken into consideration whether the patient with a one stage improvement is moving from advanced cirrhosis (4c) to stage 3 fibrosis, or from early cirrhosis (4a) to stage 3 fibrosis.

- Stage 3 encompasses many types of patients- some with few septa, and others with advanced septal fibrosis.
    - It can be challenging to distinguish stage 3 fibrosis from stage 4 cirrhosis (stage 4 with thin septa? Or stage 3?) from the small sample obtained in a biopsy.
- To be able to make a parallel with the clinical outcome, an issue is the way fibrosis and cirrhosis are evaluated and the accuracy of the scoring system used.
- How to measure that or take into account the variability within the stage is something that's been discussed but not really addressed.

- Hard outcomes are transplant, death (all-cause mortality), and decompensation events.
    - The FDA accepts two other outcomes: progression to cirrhosis (which isn't relevant for cirrhotic populations), and change in MELD score from <12 to ≥15 (substitute for listing for transplant).

C: Maybe beyond the simple numerical reversal of the stage of fibrosis, the field needs to better define a set of histological criteria that go together with a more comprehensive definition of reversal of the cirrhotic process. Perhaps if that is defined better, maybe we get closer to a state of the parenchyma where clearly we should expect less events.

- A study in *Annals of Internal Medicine* looked at patients with SVR in cirrhotic HCV- some had cirrhosis regression, and very few decompensation events. No patients in the cirrhosis regression subgroup had decompensation events.
- Another older paper describes in great detail the histological alterations that occur when cirrhosis reverses. Many things can be seen happening in the lobule: the septa get thinner; the hepatocytes start infiltrating the septa; the parenchyma returns to normal.
    - It is hard to imagine that such a sort of reversal of the whole pattern of injury is not associated with less progression of liver disease.
- Another paper by Bedossa and Columbo et al. has shown not only reversal to a lobular zonation but also the re-expression of enzyme by the hepatocytes or restoration of the zonation of the lobules with re-expression of CYP2E1.
    - In a way this proves that the function of the hepatocyte is coming back when there is regression of cirrhosis.
    - Need more accurate definition of what is regression

Q: What is the regulatory thinking on considering collagen morphometry as an endpoint? Would it need to correlate with outcomes as well or better than staging? Show less sample variability?

- There is no straightforward answer at this time.
- Can't predict what would be acceptable for collagen proportionate area (CPA) analysis. There has been overlap between stages of fibrosis and CPA in NASH, but not a large amount of data, though more is coming out.
    - If CPA matches perfectly with liver fibrosis stage, that makes it very easy, but if it doesn't, it could still be developed on its own to be a predictive tool.
    - The issue is that CPA is another assessment of histology and the field needs to move away from histology.
        - Histology is still relevant, but overall, need to develop noninvasive biomarkers that can help to see the big picture of the liver.

Q: Could portal hypertension be an appropriate endpoint?

- Patients who had thin septa were less likely to have clinically significant portal hypertension defined as hepatic venous pressure gradient (HVPG) greater than 10, and patients with thick septa that have clinically significant portal hypertension (CSPH) are more likely to decompensate.
- If histology goes from goes from thick to thin septa, correlated with HVPG, that would be a strong outcome for a patient that is regressing.
    - It is unclear if portal hypertension would be very good endpoint, as there is not that much granularity in NASH at this point.
- Once patients develop cirrhosis it can be five-ten years before they develop complications of cirrhosis. And during that time, they're developing more fibrosis, and more architecture changes. One of the things that's very clearly related to patient outcomes is their portal pressure, as measured by HVPG.
    - One problem is that not all patients with cirrhosis will have elevated portal pressure- so normalization of portal pressure cannot be an endpoint for that group.
        - It might be possible that it could work for a subgroup.
    - It is feasible, but the clinically meaningful change hasn't been defined.
    - Another problem is that it is an invasive procedure that carries a risk – and if noninvasive, very low risk methods can be found, that would be better.

C: There is a good likelihood that there are drugs that may have a potential benefit, but may not be able to show, because of the sample size needed in that particular population, the effects to show significant improvement.

- A task for the academic community is to provide regulatory authorities with data on patients with cirrhosis, that looks at those who remained cirrhotic after two or four years and those who on repeat biopsy had regression by one stage, and if there was a difference in those outcomes.
- A way to inform this would be looking at past histology data and looking for subgroups of cirrhosis with thick septa, cirrhosis with thin septa, and then looking at that information and getting prospective data in terms of what outcomes are occurring for those patients.
-

C: The FDA is not going to change position on accepting a one-point improvement in fibrosis as a surrogate – it is just not as straightforward and needs to look at the big picture.

- For example collagen proportionate area and bilirubin. If bilirubin is elevated at baseline, it would be nice to see it decrease with improvement in fibrosis.
- Once clinical outcome data is obtained, if there is data supporting that it does predict clinical improvement, it can be accepted as a validated endpoint instead of a surrogate.
- It is time to generate the evidence base to validate what is currently being accepted as a cirrhosis endpoint.
    - Some of that evidence base is not going to be generated until phase 3 and 4 data is available.
- The field as a whole needs bigger databases of the natural history of disease, preferably with as much histology data as possible to correlate with other measures.
    - FDA has a fellow working to analyze data-sets, and sponsors are invited to share their data to be analyzed.
        - FDA does not typically get datasets until a sponsor submits a marketing application.
    - There's a paucity of longitudinal biopsy data outside of clinical trials for cirrhosis because once a patient has cirrhosis, they aren't re-biopsied.
- An issue with having just the one-stage reduction is that once data comes in, it may be conflicting with other parameters that are being looked at.
    - At FDA, even if you have the primary endpoint, need to make sure that everything else looks very similar to the evidence that's being demonstrated with that primary endpoint.
        - So for example if a trial achieves a one-stage reduction, but yet the bilirubin went up or the platelets went further down, that's not going to make sense.
    - Have previously discussed a 2-stage reduction, which is a higher bar, but something that should be explored.

C: One-point improvement in liver fibrosis should be used with support of other parameters, not alone, as a surrogate endpoint for cirrhotic populations.

- Using histological features is only part of the picture, and shouldn't be relied on too heavily because of the poor correlation between fibrosis assessment in a biopsy and clinical events.
    - Other drugs that improve the prognosis of cirrhosis will not change the histology, for example beta blockers have no impact on fibrosis but do benefit the patients.
    - Need to be careful in using a surrogate the correlates poorly with clinical events, if beta blockers had to be validated with histology, these agents wouldn't be used.
    - Portal hypertension may improve without impacting histology, and would miss this information if only looking at histology.
    - Other liver function tests may be helpful to support a change in the fibrosis score.

SESSION II: PARALLEL BREAKOUT SESSIONS

European Payer Perspective

I. *CLINICAL DEVELOPMENT OF NEW TECHNOLOGIES FOR NON-ALCOHOLIC STEATOHEPATITIS: NICE PERSPECTIVE*

Presenter: Francois Maignen, National Institute for Health and Care Excellence

Slides: **https://goo.gl/YKLnv9**

This presentation represents the NICE perspective only. European HTAs can appraise the clinical effectiveness and cost effectiveness of products in different ways, and the authorization processes are not harmonized across Europe.

NICE Assessment of New Products

- NICE appraises new products and technologies for the National Health Service (NHS) based on added clinical effectiveness and cost effectiveness.
    - Appraisal process involves both clinicians and economists, who come with different viewpoints.
- NHS (and other health systems) work on a fixed budget
    - When new drugs/technologies are developed, NICE must make a decision on whether or not to recommend its use in the NHS
        - Is the drug/technology cost effective?
        - What will be displaced if a new drug/technology is recommended?
            - Who will benefit? Who will not?
- To assess new technologies, NICE computes an incremental cost-effectiveness ratio (ICER), which takes into account not only the cost of the technology itself, but includes also the cost associated with the use of the new technology.
    - For example, if the product requires hospitalization, those costs are incorporated into the calculation.
    - ICER summarizes the cost-effectiveness of a health care intervention compared with an alternate intervention or control group by dividing the difference in cost of an intervention with the difference in effect of an intervention.
        - $ICER = \frac{Cost\ A - Cost\ B}{QALY\ A - QALY\ B}$
    - ICER = the cost per quality-adjusted life year (QALY)
- NICE has defined a threshold of cost effectiveness when assessing new products.
    - Below £20,000: likely positive recommendation
    - Above £30,000: likely negative recommendation
- Elements impacting recommendations:
    - Cost Effectiveness and Clinical Effectiveness are the most important.
    - Additional Factors: Other health benefits, innovation, social value, extent of uncertainty around ICER, equality legislation
- Scope
    - Each appraisal is defined by the scope, which is comprised of four elements: population, intervention, comparator, and outcomes.
    - The scope is developed from the marketing authorization and by NHS current practice at time of appraisal.
        - Population: the population of patients that will be eligible to be treated. Generally specifies the approved therapeutic indications.

        - Product may not necessarily be recommended in this population. Could be recommended in a sub-population.
    - Intervention: the drug/technology being appraised.
        - Information provided on stage of regulatory approval.
    - Comparator: the current NHS practice.
    - Outcomes: clinical outcomes translate into improved quality of life or improved survival.
        - Outcomes converted into QALYs.

NASH-Specific Guidance

- NICE Guideline 49, published in July 2016: Describes the current standard practice in the NHS and will be the basis for the appraisal committee when considering new technology.
    - NAFLD:
        - No routine screening recommended
        - NASH suspected in higher risk groups: obesity, type 2 diabetes, metabolic syndrome
        - Diagnosed mostly on basis of liver ultrasound
            - Biopsy is not routinely offered
        - Advice on diet, exercise, and alcohol is provided
    - Advanced liver fibrosis, adults
        - ELF-test used to diagnose presence of fibrosis
            - Patients with score over 10.51 are referred to specialist
            - Can be offered pioglitzzone or vitamin E
        - Reassessment with ELF-test every 3 years
    - Advanced liver fibrosis, children
        - ELF-test used to diagnose presence of fibrosis
            - Patients with score over 10.51 are referred to specialist
            - Can be offered vitamin E
        - Reassessment with ELF-test every 2 years
- Scope:
    - Population: heterogeneous population with varying degree of severity
        - Populations in clinical trials are typically selected on basis of liver biopsy – however, this does not reflect current NHS practice.
            - Companies requiring liver biopsy will need to integrate the cost into the resources associated with the use of the product.
        - Biomarkers can be used to diagnosis the presence of fibrosis.
            - Biopsies should be correlated with biomarkers during the clinical development of the product.
        - Treatment could be beneficial for patients who have not responded to lifestyle modification.
            - Technology appraisal committee will ensure that lifestyle advice has been offered to patients- no shortcuts.
        - Consider including patients with compensated cirrhosis into population.
    - Comparator: Defined by the current NHS practice at time of appraisal.
        - No pharmacological treatment has received a market authorization.
        - If a new product receives marketing authorization and is used in the NHS, this product will become the standard of care and will become the comparator which any new product will have to demonstrate effectiveness against.

        - When designing clinical trials, prepare for the possibility that a new product will become the reference treatment to be compared against.
    - Outcomes: translatable into improved survival and/or improved quality of life.
        - Supportive of endpoints that assess evolution of fibrosis and can make a link to clinical outcome.
            - Hepatic outcomes: progression to cirrhosis, transplant, HCC, death
            - Extra-hepatic outcomes: type 2 diabetes, hypertension, kidney disease, cardiovascular disease, death.
        - Encourage patient follow-up beyond the duration of the trial and collect the maximum amount of evidence to provide more clarity to the assumptions which are integrated into the cost effectiveness model.
        - Committee will closely examine relationship between the trial endpoints and the long-term outcomes of the disease, as well as any changes in fibrosis, quality of life, survival, and resource utilization.
            - Quality of life: not very adversely affected, mostly fatigue. It is very difficult to disentangle quality of life impacts associated with NASH from other comorbidities such as type 2 diabetes.
                - Improvement in quality of life likely very difficult to demonstrate.

Economic Modelling

- Companies will need to develop a statistical model including the different health states that describe the condition that the intervention is intended to treat.
    - Health states have to be relatively homogenous in terms of disease severity and quality of life.
    - Detailed health benefits and resources measured and modelled for each health state to drive the ICER.
- No preferred economic model
    - Must detail and justify all assumptions made within model
    - Due to population heterogeneity, discrete event simulation may better capture the intrinsic variability within patients.
        - More complicated
- Liver transplant should only be included in the model for patients with advanced cirrhosis or HCC, and only patients eligible for transplant in the NHS.
    - Include a post-transplant stage
    - Include a death stage
- Consider stopping rules based on treatment response to improve the cost effectiveness in daily practice – exclude non-responders as possible.

Conclusion

- Incorporate HTA requirements, along with regulatory requirements into clinical development programs
    - Consider parallel consultation process- integrate HTA requirements early in development program (before starting pre-clinical studies)
- Develop clear value proposition as developing study design and consider where product will fit in the current treatment pathway.
- Engage with HTA agencies and regulators throughout the development process.

II. EMA-HTA PARALLEL SCIENTIFIC ADVICE

Presenter: Samuel Mettam, Boehringer Ingelheim

Slides: https://goo.gl/Ju62qf

Parallel Scientific Advice

- Boehringer Ingelheim went through the parallel scientific advice (PSA) process in 2017 for a NASH product
- In a traditional framework, sponsors engage with each regulatory and HTA agency individually. With the PSA process, all the agencies are engaged together at the same time.
- Overall Benefits to PSA:
    - EMA and HTAs are able to talk to and listen to one another.
    - HTAs are able to talk to and listen to other HTAs
        - Ideas from one HTA can be taken on by another HTA and further developed
        - Helps all parties to understand each other's perspectives and understand why particular actions are taken.
    - Increases weight of HTA advice
    - Brings the sponsor organization teams together to work on overall process instead of different internal groups working in silos of regulatory and market access.
    - Simplifies advice process by having everyone in one place at the same time.
- Sponsor Benefits
    - Actionable advice provided
    - Opportunity to discuss issues in great detail with agencies
        - Longer time to engage with all parties than if done separately.
    - Opportunity to discuss specific disease area and therapy
    - Increased understanding of the perspectives of all parties.
    - Having EMA and HTAs jointly involved increases chances of designing a trial that will meet both party's needs and requirements.
- Limitations:
    - PAS doesn't include the U.S.
        - Can do a FDA-EMA parallel scientific advice, but cannot incorporate HTAs into that process
            - PAS may not always be the right path to take and may want to engage each agency separately.
    - The advice received will vary by HTA, and it is important to bring together agencies with different perspectives to get the most value out of the process.
    - Longer process.
    - Circumstances change and what is currently true may not be by the time a drug comes to market.

III. DISCUSSION

Q: Since phase 3 trials will have accelerated or conditional approval and will not have outcomes, should trials be powered for a subgroup-analysis with ELF?

- In the EU, the likelihood of receiving conditional approval to treat a disease which is not an orphan disease is not highly likely.
- Sponsors will have to demonstrate the relationship between the endpoint and the long-term outcomes of the disease- the specific subgroup analysis is not very relevant.

- The uncertainty associated with the lack of data on outcomes will increase the uncertainty associated with ICER and decrease the likelihood of receiving a positive recommendation from NICE.

Q: Most patients present with multiple chronic conditions- how will QALYs be calculated since the likelihood of returning to a 'perfect health state' is not feasible in this population?

- The function of the QALY is to evaluate the change in health benefits between two interventions. NICE will estimate the gain in QALY that a new technology is providing compared to the standard of care in the NHS at the time of the appraisal.

C: The amount of uncertainty about what will be accepted or required in the future is challenging for developers, who feel the need to incorporate many biomarkers in the event they are validated in the future and will need to be incorporated into the design.

- Current clinical trials have histology as the primary endpoint- sponsors are also evaluating numerous biomarkers in these trials.
    - If histology data and biomarker data, such as from the ELF-test, are correlated, will that be acceptable for NICE review?
        - The technology appraisal committee will need to review evidence of the correlation.

Q: If a drug is approved using liver biopsy, that will likely go into the label. But if NICE has recommended correlating biopsy with ELF, would an approved drug be covered for patients who have only had the ELF? This is a much bigger population than patients who have had a biopsy.

- This would depend on the severity of disease and what stage patient the drug is intended to treat.
- It is fine to correlate ELF with histology as this is the way in which ELF was validated.
    - This can be presented on a subpopulation.

C: The parallel scientific advice procedure was introduced in 2010, but the percentage of sponsors that select the parallel scientific advice compared to the traditional scientific advice procedure is relatively low.

- Likely because sponsors can get traditional scientific advice from the EMA at all stages including pre clinical or early stage, and those are not as relevant to HTAs.
    - HTAs should be consulted in late phase 2 and phase 3.

C: Parallel scientific advice is valuable because it contributes to the shared understanding between both the regulators and HTAs, and also between HTA bodies.

- Payer regulations are different by country, and sometimes by region, with one country having multiple HTAs.
- This process provides ability for countries to have shared understanding.
    - Able to see what is important to each HTA body, and where there is possibility for alignment.

C: The parallel scientific advice procedure is very valuable and worthwhile, though it can take a long time and it is a great deal of work.

- In-personal oral hearing
    - Traditional scientific advice procedures do not always need an oral hearing, but all parallel scientific advice procedures have a lengthy hearing.
    - Logistically challenging – many people from multiple countries coming to attend the in-person meeting.
    - Opportunity to hear all the different perspectives is a positive, but also challenging in the sense of perspective overload.
        - Participants who do not have background in the disease area, or that do not have background in health economic issues.

Conclusion: overall support for continuing the conversation on HTA/ payer perspectives in some capacity. Whether this involves a new working group, adding HTA/ payer perspectives to existing working groups, or another alternative, will remain to be determined.

NASH Biomarker Overview

I. *CDER DDT QUALIFICATION: IMPACTS OF 21ST CENTURY CURES ACT, PDUFA VI, AND OTHER RECENT CHANGES*

Presenter: Christopher Leptak, U.S. Food and Drug Administration[1]
Slides: **https://goo.gl/UfVQuS**

Pathways to biomarker development

- Drug Approval Process: individual companies have a biomarker as part of a drug-specific program through the investigational new drug (IND) process.
- Scientific Community Consensus: tends to take a long period of time as consensus is developed.
- Drug Development Tools (DDT) Qualification Program: independent of a specific drug.
    - The three pathways do not exist in isolation and development efforts are often ongoing in multiple pathways.

Terminology

- BEST glossary: Biomarkers, Endpoints, and Other Tools
    - FDA and NIH developed harmonized glossary of terms to be used by regulatory, clinical, or scientific community with the same intended meaning
    - "Living document", opportunity to provide feedback.
    - The definitions in BEST glossary should be utilized throughout biomarker development process.

21st Century Cures Legislation

- Legislation puts FDA as an active participant in drug development, which goes beyond the traditional regulatory role.
    - Provides opportunity for more collaboration and engagement with outside parties and provide more clarity on the needs of the FDA in regards to biomarker development.
- New features:
    - Formalized submission process for three components.
        1. Letter of Intent (LOI)
            - Multi-page document with summary level information on components of development effort.
            - Looking for concise description of the biomarker and what it is. Should include information on what the drug development need is that the biomarker is intended to meet, how would the biomarker be used in drug development if it were successful, and what would be different with the availability of that biomarker versus not having it.
            - Paying close attention to the context of use.
        2. Qualification Plan (QP)
            - Focusing on analytic component of development effort.
                - White paper with additional guidance to be released.
            - Reviewing scientific knowledge gaps in drug development and how the developer intends to address them.

[1] Recorded Presentation

        - Come to agreement on what information would be collected or generated to address the gaps.
    3. Full Qualification Package (FQP)
        - Data is aggregated, analyzed, and provided to FDA who reviews it and makes a determination.
- Each component has an "Accept" or "Not Accept" decision.
    - Allows for milestones throughout the development process that allow for alignment and agreement between agency and developers.
    - Increases efficiency of the process.
- FDA required to create reasonable review timelines around the different submission types.
    - Guidance on the new timelines will be released in the next year.
- Transparency provisions
    - Under 21st Century Cures, DDT qualification becomes very public process.
    - Information is provided publically about all parties interested in tool development that are engaging with the FDA
        - Point of contact, some information about the tool under development, the context of use, and summary level information about the submission.
        - Usually multiple groups working in the same space, sometimes not aware of each other's efforts. Opportunity to increase collaboration.
    - Information from the FDA's recommendation to the developer are also made public.
        - Allows developers to review advice that has already been given, and incorporate it into their programs.
        - Increase the quality of submissions as groups learn from each other.
- Acceptance for each submission component (LOI, QP, FQP) is based upon scientific merit.
    - Needs to make the case for why the tool is important: what is the drug development need it will address, what level of information currently exists, what knowledge gaps remain, how can these gaps be addressed?
    - Needs enough information to suggest there is a decent likelihood of success.
    - Needs enough information to suggest that the proposed measurement approach is feasible.
    - Additional guidance on submission assessment will be released in the future.
- Submission Review Prioritization
    - Severity, rarity, or prevalence of disease, and the lack of alternative treatments.
    - Identification of the disease as a public health priority.

DDT Review within CDER

- Pilot Three-Tiered Internal Review
    1. DDT Program Assessment and Recommendations
        - Review by members of the biomarker qualification team
        - Ensure administrative completeness and assist developer to submit as clear a proposal as possible.

        - Not all submitters are drug developers, so also an educational piece to develop the concept and ensure the context of use is for drug development.
    2. Discipline-specific SME Assessment and Recommendations
        - Team of subject matter experts including senior level staff from the related disciplines.
            - Bring historic regulatory perspective as well as assessment of what are the needs in this space and then how the proposal might help fill that need, or if another related need might be a greater priority.
    3. CDER DDT Committee Assessment, Recommendations, and Decision
        - Committee of senior staff
        - Review recommendation of the program team and the subject matter experts and determine to accept or not accept.
- Process involves all levels of regulatory roles
    - Brings together a combination of those with very deep subject matter knowledge, and those with a higher level, broad perspective.

II. NIMBLE: NON-INVASIVE BIOMARKERS OF METABOLIC LIVER DISEASE

Presenter: Roberto Calle, Foundation for the National Institutes of Health
Rohit Loomba, University of California, San Diego

Slides: https://goo.gl/mq1xq3

Review of FNIH Biomarkers Consortium

- The Foundation for the National Institutes of Health (FNIH) was established in 1996 by Congress as a not-for-profit organization to facilitate public/private partnerships for the advancement of research for the benefit of patients.
    - Many different types of projects and initiatives, one of which is the Biomarkers Consortium.
    - The mission of the Biomarkers Consortium is to discover, develop, and seek regulatory approval for biomarkers to support and accelerate development of new drugs, preventive medicine, and medical diagnostics
        - Pre-competitive space where groups from industry, not-for-profits, government regulatory agencies can interact and work together to move the field forward.
    - Executive Committee is comprised of representatives from the NIH, FDA, CMS, industry, and the FNIH.
        - Allows direct input on what is needed by clinicians, drug developers, and regulators.
- The Metabolic Disorders steering committee has a number of biomarker projects at various stages: completed, active, in development, and pre-launch.
    - The NIMBLE (non-invasive biomarkers of metabolic liver disease) project is in pre-launch phase.

NIMBLE Project Overview

- Goal: To advance qualification of one or more, fit-for-purpose, non-invasive tools, that integrate circulating and quantitative imaging markers.
- Focus on context of use
    1. In a patient with clinical risk factors for NASH, to be able to diagnose NASH and determine the stage of disease.

        - Who needs to be treated, who is at risk, and who should be recruited into a trial
    2. In a patient diagnosed with NASH, to detect and quantify a change in NASH status and stage in response to an intervention.
        - Using current standard of biopsy
        - Allows clinical monitoring of patients, as well as the ability for companies and regulators to see if a drug is having an effect.
- Project Concept and Status
    - Structure
        - Stage 1: retrospective analysis of existing samples and imaging methodology studies
        - Stage 2: prospective study including selected markers
    - When first presented at LF5, NIMBLE was at the project concept stage. As of LF8 it is at the last pre-stage before project launch, which will occur later in the year.
    - One of the key deliverables at the end of 5 years will be to eliminate the need for liver biopsy for inclusion into a clinical trial, as well as assessing treatment response in phase 2 trials.
- Program Team Structure
    - Project Team Co-Chairs: Arun Sanyal, Sudha Shankar, Roberto Calle
    - Work Stream Co-Chairs: Claude Sirlin, Anthony Samir, Rohit Loomba
    - Project Team Members: each work stream has several team members- currently have core team and will continue to expand and invite additional academics and industry collaborators.
    - Collaborative Vision:
        - Industry-academic collaboration
        - Innovative team science
        - Focus
        - Deliverables
        - Advance the field
- Present State of Clinical Care
    - Patients with metabolic risk factors and suspected NAFLD must currently undergo a liver biopsy.
        - Patients who do not have high risk of progression are not candidates for pharmacologic therapies.
        - Patients with a high risk of progression (≥ stage 2 fibrosis) are able to be enrolled in a treatment trial.
    - Goal: to replace biopsy with a non-invasive test, or a panel of tests.
- Sharing Research Findings
    - Standardization of methodology, analysis, and interpretation
    - Publication of findings and recommending standards in peer-reviewed journals
        - Provide data freely and openly to all stakeholders
    - Collaborate with other biomarker consortia (i.e. LITMUS) to corroborate findings, and integrate emerging databases and cohorts from other countries.

III. LITMUS: LIVER INVESTIGATION- TESTING MARKER UTILITY IN STEATOHEPATITIS

Presenter: Quentin Anstee, Newcastle University

Slides: https://goo.gl/vn8uXg

Imperative for NAFLD Biomarkers

- Paradox: significant proportion of population with NAFLD, but a minority progress to advanced liver disease.
- Lack of non-invasive biomarkers has hindered diagnosis, risk stratification, and monitoring of patients.
- Lack of non-invasive biomarkers has hindered drug development and clinical trials, which must currently depend on histological endpoints.

LITMUS Concept

- Goal-oriented, tri-partite collaboration
  - Collaborative effort of practicing clinicians, pharmaceutical industry, independent academics, and biomarker researchers.
- Implementation of a robust and technologically unbiased platform to conduct the systematic study and validation of a broad range of biomarkers.
  - Working closely with EMA and FDA to ensure data produced is aligned with regulatory needs for qualification
- Ultimate goal is to establish a defined set of biomarkers that enable detection and monitoring of disease, individually or in combination.
  - Primary goal: Assisting with drug development for clinical trials
  - Secondary goal: Impacting clinical management

Funding Structure

- Funded by Innovative Medicines Initiative (IMI2)
  - Brings together funding from industry through the European Federation of Pharmaceutical Industries and Associations (EFPIA), and public contributions through the European Commission.
  - Draws on discovery science backgrounds from the two previous rounds of EU funding (FLIP and EPoS) and moves into clinical application, bringing in an expanded partner network.
    - Over 47 partners- ½ industry, ½ academic
    - Still expanding industry partnerships
  - Total budget is 32 million Euro
  - Active clinical recruitment in 14 European countries

Work Package Structure

- WP1: Project Coordination
- WP2: Methodological evaluation and evidence synthesis
- WP3: Patient Cohorts & Biobank
- WP4: Central Labs
- WP5: Imaging
- WP6: Pre-Clinical Models
- WP7: Qualification, Exploitation, and Dissemination
- WP8: Ethics
- Genuine collaboration between academia and industry with leadership from both stakeholder groups at each stage and work package.

Project Status

- Project kick off November 2017 at Newcastle University
  - 128 attendees representing all partners
- Project-specific Ethics Applications active across all 14 countries
- Complete inventory of existing biobank resources
  - Building on registry that has been recruiting patients since before 2010
  - Upgraded registry to capture richer data set
- Existing samples will be transferred to central biobank in coming weeks
- Standardized SOPs for data collection and sample handling
  - Will have highly characterized and well-phenotyped cohorts
- Registry is nearly 4,000 patients and continuing to expand
  - Due to continuing EPoS recruitment, in parallel with project-specific recruitment.
- WP5: Imaging- has developed standardized protocols for imaging which are being implemented in imaging centers across Europe.
- WP2: Methodological evaluation and evidence synthesis & WP7: Qualification, exploitation, and dissemination- have established context of use that the project will address.
- WP6: Reverse translation & pre-clinical models- drawing together existing datasets from industry and academic partners characterizing a range of models.
- LITMUS has the capacity to generate necessary clarity on biomarker validity at scale and pace and thus greatly impact drug development and patient care.

IV. LITMUS: UPDATES FROM BIOMARKER CONSORTIA- FIBROSIS MARKERS

Presenter: Detlef Schuppan, University Medical Center Mainz

Slides: https://goo.gl/wcuHpV

Importance of Fibrosis

- Possible that advanced fibrosis is the major drug development endpoint to start with
- Noncirrhotic fibrosis: non-relevant endpoint
- Fibrosis progression to cirrhosis: hard endpoint
  - Can lead to decompensation or HCC
- Need biomarkers that can indicate the presence of significant fibrosis, and biomarkers that will indicate if disease will progress quickly towards advance fibrosis.

Collagen and Noncollagen Serum Fibrosis Markers

- The aim is the development of serum or plasma fibrosis markers to:
  - Identify patients with advanced fibrosis (≥ F2) with better sensitivity and specificity than what is currently available
    - Identify patients who are most likely to progress further
  - Identify patients with high fibrogenic (and possibly fibrolytic) activity
  - Permit noninvasive selection and stratification of patients needed for pharmacological or lifestyle treatment
  - Permit noninvasive monitoring of treatment efficacy
    - Assessing antifibrotic effect on a regular basis
  - Allow short-term proof-of-concept studies with novel drugs or regimens
  - Allow personalized antifibrotic therapy

Fibrogensis in NASH

- Acute inflammatory stimulus followed by acute fibrogenic response

- Process of waxing and waning of disease
  - Fibrogenic response can wane before fibrosis is developed
  - Multiple acute stimuli and response can result in developing some degree of fibrosis that may resolve over time if the primary cause is eliminated
  - Repeated inflammation and fibrosis stimulus and response, resulting in fibrosis development and progression to cirrhosis and beyond

LITMUS Strategy and Status

- In the process of establishing and validating a panel of fibrosis protein biomarkers
- At least 6 novel fibrosis, fibrogenesis, fibrolysis markers have been selected as a core panel with the possibility to add 2-3 more
  - Validation within EPoS cohort has been initiated
  - Phase 1a cohort of LITMUS being established
- Select markers are moving forward towards regulatory approval
- Additional NAFLD biomarkers are advancing in parallel
  - Large spectrum of potential markers to compare with
- Targeted fibrosis and fibrogenesis imaging is feasible and being developed
  - In addition to refined conventional liver imaging

V. DISCUSSION

C: The two consortia are entirely complementary and work well together in a collaborative environment

- Magnitude of work is great, and having complementary efforts makes the body of work required achievable.
- Intentional overlap between initiatives – allows for corroborating findings.

C: With NIMBLE, idea is to consolidate and leverage what already exists in the literature from well-validated and phenotyped cohorts and utilize this to develop a panel combining both imaging and circulating, and possibly functional markers.

- Not developing/discovering new markers or bringing forward exploratory markers to bring to maturity – already scientifically mature
- The next step is to deploy selected markers in a prospective interventional trial which will evaluate intervention changes against pre/post biopsies

C: LITMUS has some capacity for discovery science, but the aim is not to go out and find new biomarkers. Focused on taking a broad range of existing biomarkers and assessing them fully.

- The reverse translation piece is taking biomarkers that are validated and potentially moving to qualification, and putting them back into preclinical models to determine performance.

C: The NIMBLE project (FHIH) is entirely separate from the NASH-CRN (NIDDK) – allows entry of new group of investigators and new collaboration with industry to answer the questions of the project.

- Able to collaborate with any research group or cohort, which leverages work being carried out with other cohorts and grants
- Established two goals that can be accomplished within 5-years

Q: Validating a single biomarker alone is challenging – how are the projects addressing the challenge that will come with a panel of biomarkers?

- Spending a lot of energy reviewing all the biomarkers currently available and classify them as to whether they should be brought forward.
- Selecting the best marker for a specific purpose (fibrogenesis, fibrolysis, staging, inflammatory, steatosis, etc) and then combining them into a panel.

Q: What is the role and need of big data in trying to do this type of analysis? There's going to be huge amounts of data and it's not so simple as looking at a biomarker or two.

- There are a number of different ways to look at these sorts of data sets:
  - Simplest approach is assessing the performance of a single biomarker, but there are capabilities to go beyond that.
  - With partnerships between industry and academic groups, allows opportunity to bring in those with experience in machine learning and data analytics and be able to look at the data in greater depth.
- Big data and deep learning would be critical to get to the optimal way of assessing treatment response.
  - Imaging-based collaborators who are working on AI-based technology, as well as those working on big data.

C: An important issue to consider is how to be able to include newer technology that might not be validated at the beginning of the consortia efforts into evaluation efforts- otherwise end up excluding refinements in the technology

- For example, if 2D MR elastography is approved or cleared, there should be a pathway for 3D MR elastography since it is an improvement on what already exists.
  - Collaborative effort organized by the Liver Forum involving LITMUS, NIMBLE, and the FDA has begun these conversations and discussions on these issues.
  - Hard to determine when/what tools available are "good enough"? Can't wait until have a perfect tool, because will end up waiting forever. However there are opportunities in include other evolving markers to stay current and relevant.

NASH Cirrhosis Working Group

I. *CIRRHOSIS WORKING GROUP OVERVIEW*

Presenter: Arun Sanyal, Virginia Commonwealth University

Slides: **https://goo.gl/nu8ZPz**

The goals for the first meeting for the Cirrhosis Working Group are to officially launch the group, review the past work leading to the formation of the working group, identify goals, objectives, and timelines for the group to accomplish, and define the structure of the group.

Working Group Background and Structure

- The cirrhosis working group will be composed of two sub-groups: compensated and decompensated.
  - Each group will be further divided into sub-groups, with Chairs insuring that the work is integrated/ not duplicative.
  - Sub-groups to work independently, with periodic check in with larger group to help refine.
    - Self-identification/ volunteering for the groups – group members should select one to manage the workload.
    - Chairs will identify and recruit additional academic members based on the subgroups and identified gaps in expertise.
      - Encourage involvement of junior investigators.
    - Recruit additional patient advocates to participate.
- The Liver Forum's working groups have both academic and industry leadership to guide the activities of the group.
  - Working group chairs:
    - **Compensated**: Naga Chalasani (Indiana University) and Peter Traber (Galectin Therapeutics)

        - **Decompensated**: Arun Sanyal (Virginia Commonwealth) and Jean Chan (Conatus Pharmaceuticals)
    - Integration of activities of the two sub-groups will be essential, to make sure that any outputs developed are aligned and not contradictory.
    - Balance of senior and junior investigators, to allow for mentorship and create opportunities for next generation of investigators.
    - Balance of North American and European investigators.
    - Discussions in the working group are not for attribution- place to brainstorm and talk things out freely without being construed as a formal position.
- Consensus in the group will not be forced.
    - Documents created will be based on evidence, which will either lead to consensus of not. If not, documents will state the evidence, and acknowledge gaps and additional research that needs to be completed in order to address those gaps.
    - Iterative process, multiple conference calls.

Review of Drug Development Pathways

- Regular Approval:
    - Demonstration of clinically meaningful benefit through clinical outcomes that impact how a patient feels, functions, or survives
        - Feels: symptoms, quality of life
        - Functions: impairment or improvement in ability to lead a normal life
        - Survives: liver-related outcomes, survival, hospitalization rates
    - Demonstration of clinically meaningful benefit through the use of surrogates that are generally accepted to reflect a meaningful change in health status
- Accelerated Approval (Subpart H)
    - Approval is based on surrogate endpoints that are “reasonably likely” to reflect changes in clinically meaningful outcomes.
        - Requires long-term post-approval confirmatory study to show that the surrogate endpoints do translate into a clinically meaningful benefit.
- Surrogate Endpoints:
    - Generally Accepted (HbA1c, bone density Z-score)
        - Substantial body of literature
        - Strong data quality
        - Reflects hard outcome
        - Sensitive to change
    - Reasonably Likely
        - Less data to support
        - Data quality is not as strong
        - Reasonable likelihood of reflecting change in outcomes based on relationship to biology of disease
        - Sensitive to change
    - Biomarkers that are still under development are unlikely to be accepted as endpoints.

Regulatory Science vs. Traditional Science

- Granular understanding of overall population and subpopulations
    - Risk profiles of subpopulations
    - Matching subpopulations with a drug’s mechanism of action
- Case definitions that are translatable into clinical trials
- Endpoints need to be related to clinically meaningful outcomes
    - Based on mechanism of action, biologically plausibility, sensitivity to change, best practices on how the date is collected and stored

II. DISCUSSION

Defining Populations and Subpopulations

- Both categories of "Compensated" and "Decompensated" include several distinct sub-populations, which need to be better defined.
    - There is also some gray area between compensated and decompensated where a patient does not fit clearly into one category or the other.
        - For example, patients who previously had ascites but are successfully treated are "recompensated" and categorized with compensated patients; however, they are still at very high risk of a second event, greater than that of a compensated patient who has not experienced a decompensation event.
            - Need to subcategorize and correlate to prognosis.
- Child-Pugh might not be the best way to define cirrhosis – Class A includes early stage patients as well as patients with more advanced disease.
    - There is evidence to support the use of liver stiffness as a prognostic biomarker for use in well-compensated patients, including those with NASH as etiology.
        - Could be used to identify patients at a higher risk of adverse events, irrespective of Child-Pugh.
- Most of what is known about cirrhosis is not specific to NASH, and it is important to better understand how NASH cirrhosis patients might be different from those with cirrhosis caused by other etiologies.
    - The NASH population has a much higher prevalence of diabetes and hypertension than other populations and thus come in with a different end organ profile than other etiologies of cirrhosis.
        - Due to the impact of hypertension and diabetes, it would be important to develop a standardized way of accounting for MELD score that may be driven by kidney disease as opposed to hepatic insufficiency.

Defining Endpoints

- Regulatory agencies are facing these issues now, and trials are currently ongoing. Agencies need to be able to make a decision based on current evidence, and then continue to refine it as more information becomes available.
    - Standard of care / placebo groups in ongoing trials will provide additional data.
        - NASH cirrhosis patients have the complication of many potential confounders from the treatment of comorbidities such as obesity, diabetes, etc.
- Compensated
    - Defining endpoints for compensated cirrhosis is more straightforward, there is decompensation events, transplant, death, or change in MELD score.
        - Majority of decompensation events are straightforward: ascites, hepatic encephalopathy, or GI bleed.
        - Still some gray area, including sub-clinical ascites
    - In advanced compensated population, could possibly do a trial to prove clinical benefit; however, in early compensated populations, it would be reasonable to use a surrogate.
        - Through these trials, may come to find out that there is a certain point in the natural history of disease where it is too late to change the disease progression.
- Decompensated

- Many different trial designs being proposed, and coming up with a standard for the different sub-populations would be highly beneficial.
  - Is there enough data to show that a second GI bleed is a good demonstration of progression? Alternatively, should the endpoint be a second decompensation event in another organ?
    - Possible to utilize hospitalization data
  - The criteria for diagnosing hepatic encephalopathy needs to be more clearly defined as it is one of the major endpoints reached in some of the decompensated trials.
    - Sponsors currently engaging in trials to treat hepatic encephalopathy (HE) are collecting information that will inform the definitions for endpoints.
    - Regulatory perspective has been that HE needs to be West Haven grade 2 or above for entry into the trial, and need to show improvement.
      - What clinically meaningful improvement looks like is still under consideration.
  - Delayed time to transplant is a theoretical endpoint; however, not all patients are eligible for transplant.
- All decompensation events are not equivalent- they have different mortality and different progression.
  - All events are bad, and prevention of decompensation events is clinically meaningful.
  - Should there be an ordinal scale, ranked in terms of severity?
    - Variceal hemorrhage and encephalopathy are episodic events- by treating, patients can return to compensated state.
    - Ascites is different in that it is a chronic event, and should be categorized differently.
    - Spontaneous Bacterial Peritonitis (SBP)
    - Acute on Chronic Liver Failure (ACLF)
    - Transplant/Death
  - Difference between treating the decompensation event, versus treating the underlying disease.
    - If a drug is developed to treat a complication, such as portal hypertension, it could be developed across the different underlying etiologies as long as clinical benefit is demonstrated.
      - Challenge in enrolling patients with different underlying disease due to different progression.
    - If drug is developed to treat the underlying disease, there needs to be a single etiology to treat.
  - For decompensated trials, death is likely not an acceptable endpoint, because there are multiple complications that can lead to death.

- Patient Perspective
  - QOL issues – sleep, depression, etc. are clinically meaningful for patients and collecting this information might be able to assist with identifying more patients that are on in the gray area / on the margins.
    - Things identified by patients are not always the same things identified by physicians.
  - Patient experience needs to be incorporated into collection of data on natural history of disease.
  - Not currently a good PRO tool to measure QOL in NASH cirrhosis

- Chronic Liver Disease Questionnaire (CLDQ) was not developed to regulatory standards.
    - While not validated, has been used in multiple studies and there is baseline data that could be utilized to develop an instrument for compensated cirrhosis.
- New PRO being developed- NASH-CHECK – data being presented at EASL.
    - Currently developed for pre-cirrhotic NASH but will have multiple phases to expand to cover spectrum of disease.
    - Will be part of LITMUS and therefore undergo extensive validation.
- This is an area of unmet medical need where patient advocacy groups can really drive and support development.
    - For example, PSC patient groups are currently working to develop a PRO tool.
- Use of PROMIS tool in HE and Cirrhotic populations has been shown to be an independent predictor of important events, such as re-hospitalization, transplant, and death.
    - Aggregated QOL scores demonstrate a decrease leading up to a decompensation event.
        - If refined, possible use as a prognostic marker.

Priorities for the Working Group

- Case definitions for compensated and decompensated populations
    - Compensated: identifying cirrhosis, identifying NASH as cause, sub-stratification by outcome risk
    - Decompensated: defining decompensating events, sub-stratification of decompensating events
        - Difference between addressing underlying disease vs. addressing individual complications
    - Recommendations must be from a regulatory view: quantifiable, measurable, standardized, supported by literature
- Defining primary endpoints for compensated and decompensated populations and their associated sub-populations
    - Recommendations for best practices for trial sites to evaluate patients
- Safety and management of patients with underlying comorbidities

Next Steps

- Liver Forum 9 in November (6 months)
    - Develop outline of what is known/ unknown
    - 2-3 conference calls per group
        - Identify necessary sub-groups
- Members to determine what group to primarily participate in
    - Academic members to be recruited based on expertise.
    - Recruit patients/ patient advocates in both groups.

SESSION III: REPORTS

Working Group Updates

I. STANDARD OF CARE: LIFESTYLE

Presenter: Oliver Glass, Duke University

Slides: **https://goo.gl/wmCrx4**

Working Group Status

- The first outline / draft of a manuscript of recommendations for diet and exercise in clinical trials of NAFLD has been developed
    - Importance of lifestyle management, and the challenge of comparing and contrasting different studies due to the lack of consistency of diet and exercise recommendations across clinical studies.
    - How diet and exercise influence NAFLD/NASH
    - Issues surrounding diet and exercise in clinical trials, including the complete lack of information or the lack of specific details of the diet and exercise recommendations provided in a trial.
    - Review of studies that have integrated dieticians, nutritional counseling, and specific exercise recommendations.
    - How diet and exercise recommendations are being evaluated in clinical studies.
    - Challenges and limitations.
    - Proposed tiered approach for diet and exercise, and how to evaluate within a clinical trial.
    - Summary and future directions
- The recommendations from the working group will not interfere with guidelines from the scientific societies. This is specifically for standardization within clinical trials.
- The working group also understands that it is very important to not create an intervention within an intervention.
- An important aspect for the standard of care and treating comorbidities is now to define metabolically stable, which will need to be consistent across the work of this group as well as the comorbidity management group.
- The goal for the tiered approach is for studies to be able to be compared by regulatory authorities across the board, especially as it pertains to any placebo responsiveness.
    - Looking for additional industry opinions and comments.

Discussion

C: There are two aspects for lifestyle recommendations to consider: 1.) What do you recommend people to enforce during the trial? 2.) How do you measure changes in diet and lifestyle that happen during the trial?

- The second aspect is very important to recognize and measure because they might impact the outcomes.
    - Not captures well at all currently.
- The first aspect may not be actively done in clinical studies.
    - Many do not enforce a particular diet and lifestyle change beyond recommendations.
    - It's possible to make the recommendations more precise, but it's not certain if trials, particularly early phase trials, will enforce particular changes.

    - The intent is not to mandate any intervention, rather to provide guidance on lifestyle management approaches so that studies could be compared, and developing methods to quantify such guidance.
    - Really focused on how the data is gathered, assessed for clinical trials.

C: This will only be an issue when there is a marginal effect and you think that something happened in the placebo arm.
C: We have to be sensitive to the total study burden, both to the patient and to the sponsor - diet questionnaires are not easy.

- The intention is not to create any burden, and the purpose of the tiered effect is that ultimately a sponsor can decide to not measure any of this.
- Similar to a minimum data set.

C: A tiered approach is very important as a way to have different options for people and then figure out is there a best that ultimately can improve the drug's effect in combination.
C: The FDA convened an advisory committee on dietary guidelines in 2015. And there's a scientific report available publicly, as well as an obesity guidance which will be helpful in some of these questions and in how we think to bring everything together.

II. STANDARD OF CARE: COMORBIDITIES

Presenter: Vlad Ratziu, Université Pierre et Marie Curie Hopital Pitie Salpetriere

Slides: https://goo.gl/WSzwMn

Working Group Status

- The goal of the group is to provide a broad and consensual assessment of comorbidities that are relevant for NASH clinical trial endpoints and their management prior and during NASH trials
    - Welcome additional members, particularly members with specific expertise in the broad specialties that this topic will cover.
- Brief outline of working group task has been developed
    - Description of the comorbidities that are relevant- prevalent in NASH or can impact the natural history of NASH
        - Describe to what extent decompensation or a worsening of comorbidities can impact on the severity of the liver damage
    - Review of trial conduct
        - What screening strategies and tools for measuring presence/severity of comorbidities?
            - For example, there are several formulas for measuring creatinine clearance. Which one should be used?
        - How do we define metabolically stable? This is always one of the inclusion criteria, but it must be described in more detail.
            - What are the parameters? How much variation should be allowed in months preceding randomization?
        - What are the inclusion criteria ranges that are acceptable in NASH trials for these comorbidities, how should they be measured?
            - What are the upper and lower limits that are acceptable? Sometimes this HbA1c is 9%, 9.8%, 8.5%. There needs to be consensus on this.
        - How to describe stability in the cardiometabolic drugs patients take prior to being randomized in these trials?
        - Which drugs are allowed in the trial?
            - Which ones can interfere with the mechanism of action of the drug?
            - How long can a patient be on the drug?

            - At what dose is the drug acceptable or not acceptable?
        - Which drugs are forbidden because they can affect endpoints?
        - Is a run-in period necessary?
            - When is it reasonable?
            - What are the modalities to do this?
    - Optimal management of comorbidities
        - How to optimally manage patients before inclusion
        - How to monitor comorbidities during the trial
        - How to manage comorbidities during the trial
            - How to manage possible differences in national society guidelines for global trials?
        - What is the impact on trial outcomes
    - Alcohol as a comorbidity
        - Recommendations on the upper limit of consumption and on binge drinking, how those are defined, and how much is acceptable.
    - Monitoring for cardiometabolic outcomes
        - Not directly efficacy outcomes in NASH trials, but they need to be captured and they might impact overall survival.
        - How do should they be monitored and what are the different thresholds that will need to be applied?
- Final document may not include all these topics, and needs to avoid overlap with lifestyle group.

Discussion

Q: What do the regulatory agencies want to get out of these working groups? Because it's one thing that we get out of it the ability to compare a study with another study and compare an apple to an apple. But at the same time, we have to be thoughtful about the translation of these studies to broader use.

- For example, even if criteria for glycosylated hemoglobin is set at 9.0, that's not to say that drug wouldn't be used in somebody with a glycosylated hemoglobin of 10.0, especially if it has glycemic lowering effects.
- Clinical trials are different than real life after the drug goes on the market, and that's why there is after-market surveillance and safety issues.
- The reason you need to control all these other things during a clinical trial is so that it can produce interpretable results.
    - Sponsors should try to keep populations broad in the phase 3 and phase 4 clinical trials, narrower in the beginning, otherwise you don't really see the people that are going to get the drug post-marketing.
    - The trials need to monitor and have some standard of care for the comorbidities because otherwise the results may be uninterpretable.
    - Sponsors should make sure that diet and exercise recommendations, even if they're minimal, are similar across the trial because weight loss can be the number-one driving change in histology.
    - Encourage the continuation of these groups, and try to use what management guidelines are already out there in the recommendations.
- It may be not only a question of how to standardize the population of a clinical trial as opposed to a real-life population, but it is a question of standard medical care. If a patient presents with a high HbA1c, there is an obvious need to treat and improve diabetes, but contradicts the usual inclusion criteria.
    - Some threshold has to be imposed.

C: MRI-PDFF when used as an endpoint, does not separate between steatosis from NASH and steatosis from alcohol, and steatosis from alcohol can respond differently to treatment

than NASH, and still needs to be included in the intention to treat analysis. So managing alcohol as a comorbidity is very important and should be included.

- There are simple tests now that can at least start to screen patients at baseline or during the trial—especially if there is a history of excessive alcohol consumption.

III. CASE DEFINITIONS

Presenter: Stephen Harrison, Pinnacle Clinical Research

Slides: https://goo.gl/bo1TP3

Working Group Status

- The second manuscript from the Case Definitions working group is a follow-up to the paper published previously in *Hepatology*.
- There's been considerable debate about the content and how to present the information, and it is currently being reviewed by the regulatory authorities for their feedback before it will be submitted for publication.
- Manuscript overview
    - The goal is to review the noninvasive markers that are available and try to compare or correlate them to histology and understand that ultimately right now histology is kind of a blunt instrument.
        - It's categorical variables really where the goal would be to look at this on a continuum.
        - For example, Stage 3 fibrosis isn't necessarily just a little worse than stage 2. There could be a significant uptick in the amount of collagen deposition between a stage 2-3 or a stage 3-4.
        - Can we develop noninvasive biomarkers with this continuous variable in mind, with adequate precision and accuracy that will inform hard outcomes at the end of the day?
    - Currently accepted surrogate endpoints
        - Resolution of NASH without worsening of fibrosis
            - Disappearance of hepatocyte ballooning down to zero, and resolution or persistence of minimal inflammation.
        - Improvement of fibrosis without worsening of NASH
            - Improvement by at least one stage, using the Brunt criteria.
        - The clinical significance of these changes ultimately still need to be vetted.
    - Graphical visualization
        - Graph with NAFLD severity on the horizontal axis and fibrosis severity on the vertical axis.
            - An ideal drug: drug results in resolution of both fibrosis and NASH.
                - With our current paradigm of measuring that, we could miss certain aspects of improvement if we just look at categorical variables.
            - Purely anti-fibrotic drug: drug improves fibrosis but no improvement in NASH
            - Purely anti-NASH drug: drug improves steatohepatitis and, theoretically, secondary improvement in fibrosis.
            - Undesirable anti-NASH drug: drug improves NASH but worsened fibrosis.
    - Proposed definitions

- The manuscript includes proposed definitions for: Resolution of NAFLD, Improved NAFLD, Improved NASH, Resolution of NASH, Worsened NASH, Improved Fibrosis, Worsened Fibrosis, Improved Portal Hypertension
- Includes recommendations for each phase of clinical trial
- Includes exploratory measures

SESSION IV: COMBINATION THERAPY

EU Requirements for Fixed Dose Combinations and Lessons Learned from Hypertension and Diabetes: Implications for NASH

Presenter: Elmer Schabel, European Medicines Agency/ BfArM

Slides: **https://goo.gl/QY1AiG**

Combination Treatment in NASH

- Currently entirely theoretical – EMA has not been presented with any proposal for the development of a combination treatment yet.
    - Some existing guidelines on Hypertension and Type 2 Diabetes that could have implications and parallels for NASH- since they are common comorbidities.
    - Personal opinion, not EMA opinion

Guideline on Clinical Development of Fixed Combination Medicinal Products

- Deals also with problems of combination treatment development in general
- Basic Scientific Requirements:
    - Justification of the pharmacological and medical rationale
        - Simplification of the therapy alone is not sufficient
    - Evidence needs the demonstration of:
        - Contribution of all active substances to the therapeutic effect
        - Overall positive benefit-risk of the combination
    - Evidence (which is often based on combined administration of separate active substances) presented is to be demonstrated to be relevant to the FDC
    - Establishing the contribution of each of the substances should include:
        - Identification of the population in need
        - Demonstration of the contribution of each substance
    - Therapeutic scenarios for FDCs include the following:
        1. Add-on treatment of patients insufficiently responding to an existing therapy
        2. Substitution therapy of “free combinations”
        3. Initial combination therapy
        4. FDCs with one or more new active substances
- Scenario 1 – Insufficiently treated patients (add on indication)
    - Requires the evaluation of PK and PD and the conduct of factorial design studies
    - Needs to demonstrate superiority in insufficient responders to one or more of the active substances
    - The pre-condition is the identification of an insufficient response.
    - The usual requirement would be that treatment with each of the single substances is compared with the combination.
- Scenario 3 – Initial combination treatment
    - Requires the definition of a patient population that should be specially defined

    - Justification needed that the potential disadvantages are outweighed
    - The scenario for superior efficacy comprises the following cases:
        - Two or more active substances have already an established efficacy in the target population
        - PK enhancer (of one or more active substances with established efficacy)
        - One or more of the active substance(s) has no individual efficacy in the target population (but e.g. mechanistic data suggest improved efficacy in combination)
            - Demonstration of the rationale and dose-finding may be shortened, but clinical demonstration of the superiority of the combination would still be required.
- Scenario 4 – FDCs with a new active substance(s)
    - Full PK and PD development as for a single substance is expected
    - Full demonstration of clinical efficacy (and safety) as monotherapy is usually also expected (exception given: PK enhancers).
    - The development of combination treatment in a situation with no accepted standard of care will require the full development for each of the substances as monotherapy.

Diabetes Guidelines

- General requirements for demonstration of efficacy of new substance
    - Demonstrate the superiority of a placebo in at least one monotherapy study
    - Demonstrate superiority when added to an established background therapy.
    - And/or you can also demonstrate non-inferiority to an active comparator.
- Monotherapy studies: regarded to be compulsory
    - Should use early stage patients in this scenario
    - The duration of placebo controlled should not be more than six months
    - Adequate rescue therapy should be provided
- Scenario 1- add on therapy
    - Usually reserved for patients insufficiently treated
        - Insufficient background medication, or
        - Switch everybody to a background medication and then add the new substances once they have lost response or have demonstrated insufficient response.
        - Should assure a stable dose of the background medication
        - Avoid dose adaptation during the trial
    - Rationale of the choice of the combination should be provided and be based on recommendations from learned societies.
        - It is also based on the well-established fact that diabetes is usually a combination treatment.
- Newer examples for licensed combination products
    - Standard license
        - The combination is indicated to improve glycemic control when metformin, and/or sulphonylurea and one of the mono components of the combination do not provide adequate control of glycemia
            - This is not an initial combination treatment, but usually the first standard of care, metformin and maybe also sulphonylureas are used before
    - Initial second line combination
        - Not a first line combination
        - The combination is indicated to improve glycemic control in combination with oral glucose-lowering medical products when used alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycemic control.

        - This is the newer type of combination products that use then two substances as add-on to the basic therapy with metformin
    - Initial combination (under development, regulatory assessment to be awaited)
        - VERIFY study
            - Investigates the combination of vildagliptin and metformin for initial combination treatment
            - Treatment naïve population with newly diagnosed type 2 diabetes and HbA1c between 6.5-7.5%
            - The primary endpoints are the rate of loss of glycemic control over time. And time to initial treatment failure
            - The study length is five years
- Summary
    - Combination treatment development in diabetes is well established and requires:
        - Demonstration of efficacy also in the monotherapy setting
        - Combination therapy is expected to be tested against known and well-established background medication
        - Demonstration of an insufficient response to the patient population treated.
    - There is no recommended pathway for the development of an initial combination treatment and/or the development of more than one new active substance at a time in this guideline.
    - Combination therapy programs are facilitated by the widely accepted and available biomarker, HbA1c which is also not available in NASH.
    - The last example given: the VERIFY study, has not been evaluated up to now by regulatory authorities.
        - Even if the results are positive, it is uncertain if it will lead to a license in first-line combination

Diabetes Guidelines

- General principles for study design for new substances
    - Actively controlled studies are considered gold standard
    - Placebo-controlled mono-therapy studies can be added at the end of a study in the form of a (randomized) “withdrawal phase”.
    - At least one combination study with at least one other standard antihypertensive agent is mandatory
    - General study duration recommended to be 3-6 months (at least 6 months for actively controlled studies)
- General principles for patient selection
    - Patients with mild-to-moderate blood pressure increases are suitable for studies in which current therapy is withdrawn in order to investigate the monotherapy.
    - Patients with markedly elevated blood pressure are thought to require continuous underlying antihypertensive therapy and are, thus, not suitable for monotherapy investigations.
- General principles for the primary endpoint
    - Arterial blood pressure is the undisputed primary endpoint in trials on hypertension
    - Blood pressure lowering effects of antihypertensive therapy should be documented as the pre-/post-treatment reduction of blood pressure. Systolic blood pressure is the preferred efficacy variable in this setting.
- Fixed Dose Combinations
    - Combination therapy is commonly applied in this therapeutic area
    - Usually recommended if:
        - The combination treatment is biologically plausible
        - FDCs are expected to have proven efficacy and safety for the monosubstances, as well as for free combinations

        - Demonstration of the contribution of each of the substances is expected
    - Scenarios:
        1. Initial combination treatment
        2. Second and third line treatment
            - Suitable when response to one or more mono-components is insufficient
        3. Substitution therapy
            - For patients adequately controlled with free combination
    - Scenario 1 – Initial combination treatment / first line FDCs, main requirements:
        - Initial combination treatment is usually preserved for patients with:
            - A low chance of being sufficiently treated with one agent (e.g. level of hypertension; demographic factors etc.)
            - The patient population has a high risk for CV events
        - Key elements:
            - Demonstration of safety
            - Objective: Blood pressure should be controlled in a more timely manner, in earlier time points than with the comparator.
            - Compare different doses of the initial combination with one or more late escalation arms
            - Key efficacy parameter is the time to achieve the target blood pressure.
    - Example of a newer (and only) license for an “initial” combination therapy product:
        - Viacoram: A combination of perindopril and amlodipine which was approved in 2008- decentralized license, not via EMA- (strengths: 5/5; 5/10; 10/5;
        - 10/10) with a “substitution indication“
        - Viacoram as first-line with the strength of 3.5/2.5
            - Indication granted: “Treatment of arterial hypertension”
            - Contrary to the „usual“ FDC-indication: XXX/YYY is indicated in adults whose blood pressure is not adequately controlled on XXX or YYY monotherapy.
        - As second line-therapy with the strengths 7/5; 14/10
        - First-line indication mainly granted on the basis of improved safety in comparison to the full doses of the monocomponents
- Summary:
    - Combination treatment development in hypertension is well-established and even considered an integral part of the development program
    - Combination treatment is usually restricted to the patient population not adequately responding to mono-therapy and/or standard treatment
    - “Initial combination” treatment (even including more than one new substance) is a possible way forward but requires the identification of a special patient population, as well as the use of a special endpoint
    - There is an established classification of the severity of the disease, which can be used to identify a population suitable for combination treatment
    - Combination therapy programs are facilitated by the availability of a universally accepted biomarker to be used as primary endpoint (SBP)

Lessons learned from other indications for NASH combination therapy

- The development of FDCs (and in general of combination treatment) requires a clear rationale based on PD, separate dose-finding, as well as demonstration of clinical advantages (comparative safety and efficacy)
- The development of “initial” treatment with FDCs (and combination treatment in general) is difficult in a situation for which no established treatment modalities exist

- The development of a FDC (and free combination treatment) with one (or more) new active substance(s) requires the separate, full development for the single substance(s).
- Theoretically, the development of the FDCs in NASH (or the free combination), could be done at the same time with the single substances, but is hampered for the following reasons:
    - Combination treatment is not an established principle in the disease area
    - Missing or unclear definition of “insufficient response”
    - Missing definition of an appropriate “target population”
    - Missing a well-established surrogate endpoint
- The separate evaluation of mono-therapy is compulsory in diabetes, whereas only restricted requirements apply for hypertension.
    - In NASH, there are currently no established principles but all current developments in later clinical stages use mono-therapy only
- The availability of a universally accepted biomarker is the basis of the requirements in both disease areas.
    - Such a marker is currently not available in NASH.
- It is well-established for both diabetes and hypertension that “insufficient response” patients are candidates for combination treatment.
    - Such criteria have not been established in NASH, but might be developed on the basis of the currently discussed histology response criteria (e.g. any deterioration of NAS score and no change in fibrosis stage).
- The development of combination treatments in hypertension also includes the possibility to investigate “initial combination” but requires the identification of patient population with high medical need.
    - Can such a population be identified in NASH? (e.g. could it be a fibrosis stage III/IV population with high NAS activity?)
- In arterial hypertension, the design of “initial combination” treatment trials uses an endpoint different from the established endpoint
    - Can such a requirement be transferred to the clinical situation of NASH patients? (If it is the above population, the endpoint could be decompensation events?)
- All these considerations refer to efficacy only. The demonstration of an acceptable level of safety, however, remains a potential issue.

FDA Regulatory Considerations for Co-Development of Two or More New Investigational Drugs for Use in Combination in NASH

Presenter: Stephanie Omokaro, U.S. Food and Drug Administration

Slides: https://goo.gl/E9AA62

Presentation Overview

- Two or more new drugs that have not been previously developed for any indication to be used in combination to treat a disease or condition
- Not intended to apply to development of fixed combinations of previously approved drugs or to development of a single new investigational drug
- Not intended to apply to development of combination products comprised of two or more different types of medical products (e.g., drug and device, drug and biological product, or all three together). (See 21 CFR Part 3)

Fixed Combination Prescription Drugs for Humans (21 CFR 300.50)

- Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects
- The dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy
- Often factorial studies are needed to show the contribution of each component of a fixed-combination drug

Rationale for Combinations

- Multiple therapeutic targets to provide greater effectiveness than either ingredient alone
    - Either by having a greater effect for a single indication or by treating more than one indication
- Minimize adverse events
    - Having one active ingredient enhance the safety or effectiveness of another active ingredient
- Minimize development of resistance (more durable response)
- Patient convenience
- Facilitate compliance with a prescribed regimen
- Minimize the potential for abuse of an active ingredient

Regulatory Concerns and Challenges:

- Information on how each ingredient in a combination contributes to the effect of the combination is a fact “material” to the consequences that may result from customary use of that product
- It is within FDA's authority to require testing as is necessary to establish the safety and effectiveness of ingredients used in combination

Qualifying Criteria

- Strong biological rationale for use of the combination
- A full nonclinical characterization of the activity of both the combination and individual new investigational drugs or short-term clinical study on established biomarker
- A compelling reason why the new investigational drugs cannot be developed independently
- Stepwise approach:
    - Determine whether co-development is an appropriate development plan
    - Nonclinical co-development
        - Demonstrate the biological rationale for the combination
        - Nonclinical safety characterization (ICH M3, R2, S9)
    - Clinical co-development
        - Early human studies (Phase I): safety of individual drug, safety and dosing of combination
        - Clinical Pharmacology: PK, bioavailability of each drug separately
        - Proof of concept studies (Phase II): contribution of each drug in the combination and combination itself
            - Dose finding prior to phase III: important to refine the combination dose or doses and select dose(s) for phase 3 trials
            - Test multiple doses of both drugs for optimal combination- if one is more active than the other, multiple doses of more active drug
            - Study multiple doses of drug to find which one is more toxic
    - Phase III studies
        - Design will be determined case-by-case based on effects of combination and individual drugs, the feasibility of monotherapy and SOC
- Scenarios:

  - Scenario 1: each drug has activity and can be administered separately. The factorial study design would not only involve the combination but each drug individually and then standard of care.
  - Scenario 2: each drug cannot be administered separately, therefore it's only the combination that's compared to standard of care
  - Scenario 3: one active drug and the other is inactive and they can be administered separately. Only testing the active drug individually.

Regulatory Considerations:

- There are revisions being proposed for the current guidance (https://www.federalregister.gov/documents/2015/12/23/2015-32246/fixed-combination-and-co-packaged-drugs-applications-for-approval-and-combinations-of-active)
  - Existing regulations in subpart B of part 300 (21 CFR part 300) on prescription fixed-combination drugs being revised
  - New provisions applicable to prescription and nonprescription fixed-combination and co-packaged drugs
  - Harmonize requirements for prescription and OTC products and make them consistent with FDA's long-standing policy
  - Specific evidentiary requirements must be met for approval
    - Ensures therapeutic purpose of all active ingredients, even those that might not be considered active ingredients in other contexts, is claimed
    - Amount and type of data and information needed may vary depending on a number of factors, including the therapeutic intent of the combination
    - Scientific justification for the testing and data that might be needed must be provided
  - Sufficient evidence must be provided to demonstrate that product meets the requirements of § 300.53(a), including demonstrating:
    - The contribution of each active ingredient to the effect(s) of the combination
    - That combining the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients
- Exceptions
  - For products which it would be infeasible or medically unreasonable or unethical to meet the requirements of the proposed rule:
    - Proposed § 300.60 would give FDA the authority to grant a waiver of some or all of the requirements of the proposed rule at the request of an applicant or interested person or on its own initiative
  - Products such as whole blood, individual or pooled transfusable blood components (e.g., pooled platelets), pooled plasma products, and plasma derivatives from human or animal sources (e.g., immune globulins) would not be regarded as fixed-combination drugs

Factorial Studies

- When Needed:
  - Generally the preferred design to support use of a combination
  - Combinations, in which the effect of each active ingredient is directed at the same sign or symptom of a disease or condition (e.g., similar mechanisms of action):
    - Need to demonstrate that the combination has a larger treatment effect than one or more of the active ingredients alone
  - Combinations in which one active ingredient is intended to:
    - Provide a direct effect that either potentiates or makes another active ingredient more tolerable
    - Minimize an adverse reaction associated with another active ingredient

        - The trial would have to establish enhanced safety or effectiveness of the combination versus the disease-active ingredient alone
    - A factorial study is unlikely to be needed to demonstrate the contribution of each active ingredient in a combination where the active ingredients are directed at different signs or symptoms of a disease or condition or at different diseases/conditions:
        - Evidence that demonstrates that the active ingredients are effective individually and do not interfere with one another (e.g., pharmacokinetic data) may be adequate
        - Each component expected to have its usual, independent effect on a particular symptom/disease, and would not be expected to affect the other symptoms/diseases
- Limited Utility:
    - Practical constraints on the use of a factorial design as the number of active ingredients in a combination increases
    - The greater number of components in a combination, the greater number of comparisons needed to demonstrate each claimed effect
    - At some point, a factorial study design may become infeasible
    - Overall power of a factorial study equals ~ the power of the individual comparisons raised to the n^{th} power where n is the total number of comparisons
        - Each individual comparison in a factorial study should be sufficiently powered so that the overall power is at least 80%

Barriers to Co-Development

- Demonstration of individual contribution
- Less information about clinical safety and effectiveness and dose-response of the individual new investigational drugs
- Lack of flexibility in adjusting the dosage of each active ingredient to an individual patient's needs
- Possibility of overexposure, or unnecessary exposure to a particular active ingredient

Lessons Learned from Oncology

- Combinations of targeted agents a high priority in oncology
    - Resistance to initially effective single agents often develops quite rapidly in many adult tumors
    - More than 100 combination trials initiated since 2000
    - Facilitated by the Intellectual Property (IP) language in Cancer Therapy Evaluation Program (CTEP)-industry agreements
- Molecular-targeted effects:
    - Mechanism of Action/Proof of Principle
    - Biomarker assessment and evaluation, assay development and qualification
- NCI/CTEP Approach
    - Molecularly targeted combination studies are the future of personalized medicine
    - Combination strategies are critical to improving therapeutic outcomes
        - Rational combination of agents
        - Properly selected patient population
    - Trials designed to maximize inhibition of a critical target or target multiple cellular pathways in cells
        - Tumor cell eradication
    - NCI uniquely positioned to perform novel agent combination trials by overcoming regulatory, intellectual property, and risk aversion hurdles because of its extensive collaborations with industry and academia
    - CTEP's Regulatory Affairs Branch (RAB) is focused on:

        - Developing partnerships with industry and academics that allow for co-development of novel therapeutics and on assuring that CTEP meets all its regulatory responsibilities with the FDA regarding INDs
        - Facilitating interactions between the FDA, NCI, and Industry
        - Coordinates FDA-NCI Monthly Meeting with the FDA Oncology Director and staff
            - Discuss issues of common interest related to oncology drugs and their approval, with the ultimate goal of streamlining drug development
            - There may be correlates related to NASH that could be discussed with NIH
    - CTEP Activities
        - Preparation and submission of Investigational New Drug Applications (INDs)
        - Review of protocols/protocol amendments
        - Liaison with FDA, intramural and extramural investigators, pharmaceutical companies
        - Preparation of agreements (CTAs and CRADAs) for clinical development of agents
        - Coordination of company interactions with NCI and investigators
        - Preparation of MTAs for basic research with investigational agents in clinical trials

Antiretroviral Experience

- Historical Perspective
    - There were over 10 years of monotherapy in the treatment of HIV prior to going into combination treatment.
    - Initial combination treatments were on approved drugs.
    - It wasn't until 2000 or even 2004 that it began to combine not only approved drugs but approved drugs with investigational new drugs.
    - It has been a stepwise approach for that disease condition as well.
- Combination Experience with Antiretroviral Drugs
    - Biologic rationale is to target different metabolic pathways or different steps in the replication cycle of the pathogen
    - All currently available combinations approved on basis of bioequivalence of the combination to individual component drugs taken together, after approval of all individual drugs
    - Existing data from approved drugs used to demonstrate the contribution of the individual active ingredients including clinical data on use of the individual ingredients in a combination, in clinical pharmacologic data, and in nonclinical data
    - New clinical data would ordinarily be needed only to demonstrate that the bioavailability of the fixed-combination drug is comparable to that of the active ingredients administered individually

Conclusions

- Fixed drug combinations of new investigational products present a challenge because individual components are not well characterized.
- Development is inherently more complex and requires studies to characterize not only the combination but also the individual agents to the extent necessary and feasible.
- Early engagement with FDA is critical.
    - Consulting on the appropriateness before initiation of clinical development of a combination and as needed throughout the development process.

Discussion

Q: How are regulatory agencies thinking about labeling drugs for approval as monotherapy? Would that be "drug A is approved for the treatment of NASH F1-3"? Or would it say "approved for the treatment of fibrosis NASH 1-3 and caused complete regression of steatohepatitis or inflammation but no change on fibrosis", for example?

- Relatedly, how will combinations be labeled in this example?
- It would be expected that a compound that reduces inflammation will also influence fibrosis development, but if it doesn't, the correct indication would likely be "treatment of F2 and 3 NASH".
    - However, in a fibrosis drug where there is no influence on inflammation, this would have to be labeled differently, because it is not treating NASH, it is treating fibrosis in NASH.
    - Premature to answer from a regulatory perspective- prescribing information is driven by data, so the data that come out of the phase 3 trials will inform how the label is written.
    - It's possible it may be similar to how the primary endpoint is defined right now for phase 3 trials
        - Improving inflammation and no worsening of fibrosis or vice versa, that may be wording that would be appropriate
    - It's possible that a drug that treats the inflammatory component would be labeled as "treatment for NASH" with a second sentence "this drug has been approved under accelerated approval and has not shown to affect fibrosis or clinical outcomes."
    - If a drug treats only the fibrosis component, it would likely be an indication for the treatment of liver fibrosis secondary to NASH. There would likely be a second sentence that says, "there was no effect on the underlying NASH process and it was approved under accelerated approval and it hasn't shown effects on clinical outcomes."

C: The treatment of fibrosis is important because that really drives a lot of our thinking. Do you expect that the insult or the metabolic dysregulation, the inflammation is all driving the fibrosis? That could be something that you could think more along the how you develop the drugs and put them in combination and show the combined efficacy.

C: It was great to hear from the regulators more clarification around the potential indications, and it makes a lot of sense. And since the agency wisely has looked at two potential endpoints for the approval under subpart H, one could look at combining drugs that affect more fibrosis or more steatohepatitis and then looking at co-primary endpoints.

- Could actually demonstrate the benefit of the combination versus the individual components on each one of those respective endpoints as a potential way to actually look at the benefit.
- There is actually a third endpoint, though no one has yet chosen it, but it is improvement of both steatohepatitis and fibrosis.

C: Since the guidance documents aren't there, the field should think outside the box and broaden our thoughts on combination therapy.

- Sequential therapy needs to be thought about where there are drugs that may hit right up front really hard – these might not be the best to use chronically and can go to more of a chronic maintenance. There are drugs and combinations out there that we should start thinking about that.
    - Combination doesn't have to be fixed dose- there's plenty of examples of induction therapy followed by maintenance in other therapeutic areas.
- There's a statement from regulators that sponsors shouldn't be studying drugs that have potentially a different indication such as a diabetic drug- but what about drugs that actually have the potential to have labeling for both?

- Using the example of either liraglutide or semaglutide that may actually end up being a diabetic drug that also has a NASH indication and that should still be allowed to be studied as a combination therapy.
- Using already approved drugs in a combination wasn't addressed in the talk- there is not a problem with using already approved drugs. Many drugs under development are either diabetic or dyslipidemia drugs being repurposed for NASH.
    - Wasn't addressed because it is easier to do a combination study in a drug that's already approved.
    - If it's approved for a different disease, it wouldn't necessarily remove need to do an efficacy factorial study. But there wouldn't be as much safety issues.
    - Factorial studies are not needed for every situation, it's ok not to do factorial design if you have different diseases where you know what the effect is going to be or that there are going to be separate effects that do not interfere with each other.

C: There is a growing graveyard of direct antifibrotic drugs, and many of them may have a signal that is just being missed because they are not being used in combination. We may be missing opportunities by not thinking outside the box of how to really address those combinations.
C: One of the points that stuck out was identifying patients who have a high unmet medical need and targeting them for combination. Gilead's approach with combinations is to target patients who have a high unmet need- F3, F4 patients.

- These patients probably have a low likelihood of responding to at least first-generation monotherapies, at least from an antifibrotic perspective, so the approach with combinations is to start in those patients, and to start with combination treatment as opposed to starting with monotherapy and then going to combinations.
- Relates to differences between NASH and diabetes and hypertension, where NASH doesn't have a good biomarker. It's less attractive to do a study where patients are biopsied again after one year on monotherapy and demonstrate that they've progressed and then start combination therapy.