Forum for Collaborative HIV Research
Liver Forum 4
Thursday, 14 April 2016
Barcelona, Spain

Opening Remarks (Please see slide set: Welcome and Project Overview: http://www.hivforum.org/storage/documents/2016/LF4/liver%20forum%204.%20introduction%20and%20overview.pdf

Veronica Miller, Executive Director, Forum for Collaborative HIV Research and Liver Forum

Introduction

- The purpose of the Liver Forum is to enhance drug development so that new interventions or candidates for therapeutic can be developed most efficiently to benefit patients
- The Liver Forum promotes increased clarity, efficiency, and collaboration by decreasing uncertainty, redundancy in development, time and risk.
    - Multi-stakeholder partnership that enables adaptive management
    - Informal organization but structured enough to get things done
    - Liver Forum members are representative of all stakeholder groups
        - Non-competitive, safe environment
        - Synergy vs. duplication
        - Transparency
        - Information democracy

Liver Forum Educational Mission

- Committed to fostering professional development, training the next generation of leaders
    - Principles of collaborative drug development and regulatory science, trans-atlantic context
- Opportunities to engage junior faculty, fellows, and interns in the work we do
- Current "Liver Forum Trainees":
    - Yuval Patel, Duke University/clinical fellow with Andrew Muir.
    - Mohammad (Shadab) Saddiqui ,Virginia Commonwealth University/junior faculty with Arun Sanyal
    - Lauren Smith, UC Berkeley/MPH intern with Veronica Miller.
    - Shruti Tibrewala, UC Berkeley/ MBA/MPH intern with Veronica Miller

- **Opportunities open** for additional trainees – Europe, other US universities, industry
    - Please contact Veronica Miller

Historical Overview + Accomplishments

- LF#4 – short history since LF#1 in Boston, 2014
- Meet twice a year in conjunction with the AASLD and EASL conferences
- Established a safe space for informal exchange of the regulatory perspectives from both the EU and the U.S.
- Many collaborations started among Liver Forum members

- Three manuscripts in preparation for publication
- Liver Forum approximately 69 industry members

Thanks and Acknowledgements

- All financial sponsors (Please see slide set/website for sponsor list)
- Liver Forum Steering Committee (Please see slide set/website for Steering Committee members)
    - As described in our Articles of Governance, SC industry membership rotates on a two-year cycle to distribute leadership opportunities
- Forum staff:
    - Malene Cobourne
    - Jeff Kaminski
    - Brenda Rodriguez
    - From UC Berkeley: Lauren Smith and Myrna Cozen
- Logistics planners: Prism Event Management
    - Paula Blay, Graham Hill, Ash Lawson, Mairead O'Reilly, George Seaton

Overview of LF #4 program

- Update on Forum activities
- Regulatory update
- Discussion of next steps
- Special presentations
    - Gathering data
    - Analyzing data

Welcome from SC Co-Chairs

Arun Sanyal, MD, Arun Sanyal, MBBS, MD, FACP Virginia Commonwealth University,
Center for Clinical and Translational Research
Gary Burgess, MBChB, MMed, MFPM, Vectura Limited

- We have seen tremendous growth in the Forum in just over a year and we continue to become more engaged
- To reiterate the points that Veronica made:
- The primary objective of the forum is to catalyze the pathway to development and regulatory science
    - not meant to replace the hardcore research that is presented at EASL and AASLD, which have been very good partners to the Forum and with which we will continue to build synergies
- The second objective is our commitment to launching the careers of young people
    - We need hepatologists who have formal training in both hepatology and regulatory affairs to build capacity for our societies and for the next generation.
    - For those of you from academia, please let us know if you have young scholars who would like to get involved with Forum activities

- Highlight: recent teleconference where we discussed the regulatory implications for development of drugs in NASH
    - About 160 people participating
- To all industry colleagues: get involved in the different work streams
    - A rewarding and a very good experience as far as industry is concerned

Regulatory Updates (Please refer to slide set):
http://www.hivforum.org/storage/documents/2016/LF4/liver%20forum%204.%20regulatory%20updates.pdf)

Elmer Schabel, MD, EMA German Division (Bundesinstitut für Arzneimittel und Medizinprodukte)
Lara Dimick-Santos, MD, FACS, U.S. Food and Drug Administration

- This is a regulatory update on the status of drug development programs for NASH in Europe, accepted by CHMP, including
    - Current proposals for study design, populations and endpoints in clinical trials for NASH (please see slide set for the specific proposals being considered for each of these factors)
    - Problems identified: Interim endpoint, final endpoint, safety evaluation, statistics
        - Some of these already identified in the recent Liver Forum teleconference Q+A session
- Regulatory experience in Europe is very limited
    - Only two Phase 3 clinical trials have been presented before CHMP since 2012
    - Greater number of advice procedures
    - One development program has been presented to the NCA Germany
- Therefore, these are preliminary conclusions and are open to change in the future

<u>Study Design</u>

- High unmet medical need is acknowledged in Europe
- One accepted study design we discussed previously is compliant with European regulations
        - presented at the last Forum meeting
    - Two-stage design with an interim analysis on surrogate endpoints
    - Final analysis with hard outcomes
    - Interim analysis could lead to a conditional approval, the condition being that it is confirmed by the final evaluation and demonstration of clinical benefit with the hard outcomes
    - Trials will be ongoing at the time of the final decision about marketing authorization
        - Implications (see below)
- Currently, no proposal for a seamless Phase 2 to Phase 4 trial design submitted
    - Lara described this approach at LF#3
- Generally, it is accepted that only one pivotal trial is required
    - consequences (see below)

<u>Patient Population</u>

- The inclusion criteria: active NASH, NAS score of at least 4

    - main focus on patients with fibrosis Stage 2 and 3
- Questions re fibrosis stage 1
    - Included or left aside for the time being?
    - Are they suitable for demonstrating a benefit at all?
    - Will F1 patients be treated after licensing despite not having been studied?
        - Labeling issue, which must be addressed
    - Development programs that we have seen and accepted include an exploratory cohort of stage 1 patients, with main focus is on Stage 2 and 3
- Exclusion of Stage 4 patients is acceptable, although we don't know whether reversal of cirrhosis is only difficult or impossible

Interim and Final Endpoints

- Two composite, co-primary endpoints for interim analysis have been accepted:
    - composite of complete resolution of steatohepatitis and no worsening of fibrosis stage
    - composite of one point improvement in fibrosis stage and no worsening of steatohepatitis.
- These are ideal endpoints: evaluate different aspects of individual response and response at the population level
- There will be times when it is not possible to achieve this endpoint
    - Some unknowns: interdependence of inflammatory changes and fibrotic changes and their alteration by intervention
- The endpoints at interim analysis have to be sufficiently strong to conclude there is a positive benefit risk balance
    - legal condition for a conditional approval for Europe
- The final endpoint is based on a composite of death, liver transplantation, cirrhosis-related clinical events, and histological diagnosis of cirrhosis
    - Evaluation is event driven, not based on duration of trial
        - The trial goes on until the pre-planned number of events occurs
- Noninvasive, regular screening for cirrhosis is acceptable as a strong, surrogate event, however main efficacy conclusion is based on the occurrence of histological evidence of cirrhosis
- List of cirrhosis related events should be as completed as possible
    - Bleeding events, encephalopathy, etc
    - HCC
        - May be controversial
- Death includes all cause mortality, not just liver-related mortality
- The inclusion of prognostic scores (e.g., MELD) into the composite is acceptable

Further Study Design Considerations

- Study design should clearly define concomitant or past treatment for comorbidities, including diabetes medications, counseling and other "treatment" for obesity, prior or concomitant use of "NASH" treatments, including: Vitamin E; metformin, pioglitazone
- Central lab evaluation of liver histology is welcomed
    - whether necessary is still debated
- Problems with serial liver biopsies
    - The more biopsies that are pre-planned, the more likely to have missing data

- Thus, aim to have as complete a data set for the interim analysis as possible
    - Missing data later cirrhosis diagnosis could be more acceptable
- Can the interim evaluation account for different mechanisms of action (MoA)?
    - E.g. if MoA is anti-inflammatory only, it might not be possible, within a reasonable timeframe, to demonstrate the required decrease in fibrosis score
- Current CHMP opinion: composite of NASH resolution/no worsening of fibrosis not considered sufficient
    - At minimum, expect co-primary evaluation
        - Ensure that the overall endpoint does not depend on one feature of the composite
- Should have a proof of no increase in fibrosis and the resolution of NASH
    - If difference with Phase 2 data, the solution is to prolong the observation period
- Continuing conduct of study after interim results become available/product is licensed
    - Enhanced measures to prevent increased drop-outs
    - Issues with maintenance of blinding
    - Implications for recruitment strategies

<u>Safety Evaluation</u>

- See "Reflection paper on assessment of CV risk of medicinal products for the treatment of cardiovascular and metabolic disease"
    - Is this applicable to NASH?
- Consider the paper, but flexible approach possible, depending on mechanism of action, and phase 2 safety results (metabolic parameters and metabolic biomarkers)
- CV risk
    - CV outcome study generally not expected
        - Inclusion of all-cause mortality partly takes care of concerns
    - MACE and MACE-plus endpoint are recommended
        - Meta-analytic approaches
    - Exclusion of thresholds for CV events (e.g. diabetes) not considered necessary, unless indicated by phase 2 data

<u>Statistical Considerations</u>

- Splitting of the type 1 error (including asymmetric split) is considered acceptable; including one which shows a stronger level of evidence for the interim analysis than for the final (i.e., 0.01 and 0.04)
    - The split itself does not account for the fact that only one study is presented
        - Independent confirmation required
- CPMP/EWP/2330/99 ("One Pivotal Study Guideline)
    - Increased requirements if only one trial
    - Concordance across subgroups
    - External validity
    - More extreme levels of type 1 error
        - The type 1 error should be at least half of what was expected at interim and final for two trial programs
- Using results from interim analysis for sample-size recalculation for final evaluation

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- Phase 2 data usually do not confer valuable data on the final endpoint
  - No indication of the rate of occurrence of cirrhosis nor of the clinical events that will be measured
- Acceptable to look at rate of events for the purposes of establishing final study size.
  - Blinding may be difficult
    - Type 1 error control may become an issue
- The estimation of the final number of events occurring assumes a linearity of these events, which might not be true
- At the end of the trial, may have more events presumably
  - linearity assumption is thought to be conservative and, therefore, acceptable

Comments by Lara Dimick:

- Conditional approval, as outlined by Elmer, would be the equivalent as accelerated approval by the FDA
- We agree on endpoints, populations, and the clinical benefit endpoint
- There is some debate between the two entities about whether hepatocellular cancer (HCC) really belongs as a clinical benefit endpoint
- There is some question about the safety endpoint, especially with regard to an anti-inflammatory drug, however that can be discussed based on the mechanism of the drug

Questions/Comments and Discussion:

Q: RE long-term post-approval, natural history and placebo arm based cohorts: should liver and cardiovascular data be collected? What is the control population?
Discussion

- Yes, CV/metabolic events should be collected and adjudicated as a safety assessment. A signal would indicate need for cardiovascular outcomes trial. At this time, we don't have sufficient natural history data, thus placebo controls still under consideration.

Q: Should all-cause cancer (observed in excess mortality studies) be captured as a safety event?
Discussion:

- Yes
- All these considerations on the ongoing trial in the long-term, and on the integrity of the trial after the interim, and after licensing, are based on the assumption that a placebo control is included in the trial design. Only then do these concerns apply fully.

Q: How can the integrity of the study be maintained after accelerated or conditional approval? Any thoughts about compliance to treatment for patients in a placebo arm, after one or two drugs are approved and reported to be efficacious? Might it depend on the MoA of the approved vs. investigational drug?
Discussion:

- It will be difficult to maintain a control trial after the first drug is approved. If the new drug seems to have less side effects and better efficacy, that might be an incentive for patients to enroll in a new trial

- That would be the time to rethink trial designs: once a few products have undergone all the procedures and validation data are available from the interim endpoint, and if they indeed correlate with the hard outcomes
- A surrogate reasonably likely to predict can turn to a validated surrogate with controlled clinical trials, such as happened with viral load in hepatitis C. However, the existence of approved drugs for a disease may eventually change the status of "unmet medical need" which could impact eligibility for accelerated approval
- We will likely need combination treatment with different MoAs to fully address the "unmet medical need"

Q: Regarding the alignment of accelerated approval in the US and the PRIME process for CHMP in Europe -- what are the clear misalignments at this point? Are there specific examples, of when you would allow submission of an accelerated approval with the EU versus FDA?
Discussion:

- The PRIME ("proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines" – see LF3, Schabel presentation) mechanism is not an exact parallel to accelerated approval, rather, a mechanism to fill the gaps with regard to priority, designations, etc. It includes an early assessment -- the assessment period is shortened before a decision is made
- The PRIME program is more like fast track and priority review. Conditional approval is more like accelerated approval. They are pretty similar in the way we use them at least for NASH

Q: Going back to the question of unmet medical need once new drugs are approved. If a placebo response rate is 20 percent, and the active arm rate is 50 percent, clearly better than placebo and the compound gets approved, that still means 50 percent of people who need therapy have no options. Is that still then considered unmet need met or it's still unmet?
Discussion:

- That would still be an unmet medical need, such as PBC, but once we have multiple drugs on the market, we eventually get to the point where it is no longer an "unmet" medical need

Liver Forum Working Group Updates

Disease Definitions Working Group
Co-chairs: Sophie Mégnien and Stephen Harrison
Subgroup Leads: Manal Abdelmalek, Quentin Anstee, Vlad Ratziu, Laurent Castera, Scott Friedman, Brent Tetri
Reporting: Shadab Siddiqui, Virginia Commenwealth University

Please refer to the following slide set:
http://www.hivforum.org/storage/documents/2016/LF4/liver%20forum%204.%20liver%20forum%204.%20disease%20definitions%20for%20nafld.pdf

Moderators' Introduction: At LF3 we arrived at consensus regarding the need to reduce the number of provisionally proposed disease stages down from the seven and to synthesize those remaining in a meaningful way that would have clinical impact moving forward in trial development. Dr. Siddiqui has done a masterful job of pulling this together into three different subsets and he is going to take us through those now.

Introduction

- Nonalcoholic fatty liver disease (NAFLD) is a histologically diverse entity
  - Lack of consensus on definitions
  - Multiple histological scoring classification systems
    - unclear which of these lends itself best in the context of regulatory science
  - Limited guidance regarding the use of biomarkers and diagnostics in regulatory development
- WG Goal: to improve the efficiency of the regulatory approval process
  - Clarify stages of NAFLD for future clinical trials using both histological and noninvasive methods
  - Comprised of members from regulatory agencies (FDA and EMA), professional societies, regulated industry, including pharmaceutical and diagnostic technology companies representatives, and representatives from academia
  - Members assigned to subgroups corresponding to provisionally defined stages of nonalcoholic fatty liver disease
  - seven subgroups were identified and each was assigned a subgroup lead:
    - isolated hepatic steatosis, led by Dr. Abdelmalek
    - indeterminate NASH, led by Dr. Harrison
    - definite NASH, led by Dr. Anstee
    - NASH with early fibrosis, led by Dr. Ratziu
    - NASH with advanced fibrosis, led by Dr. Castera
    - NASH with compensated cirrhosis, led by Dr. Friedman
    - NASH with decompensated cirrhosis, led by Dr. Tetri
- Each subgroup considered their respective disease stage in terms of clinical phenotype histology (grade, activity, fibrosis stage), and available means of non-invasive assessment
  - Subgroups reconvened for a consensus building process (presented at LF3)
- Today's presentation describes follow up work based on discussions during LF3

- NAFLD/NASH categorization
  - Disease states were consolidated into three major categories, each comprising two or more subcategories
    - NAFL
    - NASH
    - NASH-related cirrhosis. Each of these categories comprised two or more subcategories

NAFL Diagnosis

- The minimal histological diagnostic criteria: ≥ 5% hepatic steatosis
  - Patients meeting this criterion can have minimal lobular inflammation
  - Exclusion: cytological ballooning or significant fibrosis
- Subcategories within NAFL, include
  - isolated hepatic steatosis
  - indeterminate NASH
  - Steatofibrosis
    - defined by presence of hepatic steatosis and significant fibrosis in the absence of lobular inflammation or cytologic ballooning
- Compared three histological scoring systems for NAFL:
  - NASH CRN
  - SAF
  - Goodman (please see slide #9 in this slide set)
- Each system evaluated by following criteria:
  - Objective?
  - Subjective?
  - Quantifiable and replicable?
  - Sensitive to change?
  - Externally validated?
  - Previously used in clinical trials?
- Based on this evaluation, the NASH-CRN scoring system appears to be the most robust criteria for assessment and diagnosis of NAFL

NAFL Non-Invasive Biomarkers

- Similar comparisons
  - Noninvasive models, constructed using readily available clinical information like the NAFL liver fat score or the hepatic steatosis index
  - Serum biomarker (CK-18)
  - Ultrasound
  - CAP (controlled attenuation parameter)
  - MRI and MRS
- None of these criteria is able to distinguish NAFL from NASH or to differentiate subtypes of nonalcoholic fatty liver
  - Focus on the to quantify hepatic steatosis
- First four:
  - limited by ability to accurately quantify various stages of hepatic steatosis
  - not used as primary endpoints in clinical trials
- MR-based technology
  - Can quantitate hepatic steatosis with significant accuracy
  - Used as primary endpoints in clinical trials
- Only MR-based technology is sensitive and specific and has been shown to change over time, and, therefore, it is the biomarker of choice for documenting nonalcoholic fatty liver noninvasively

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NAFL Summary

- Minimal histological criteria necessary to diagnosis NAFLD is the presence of ≥ 5 % hepatic steatosis
    - Can have minimal lobular inflammation.
    - Presence of cytologic ballooning or fibrosis excludes NFL diagnosis
- Of the three histological scoring schema, NASH CRN is the most validated
- SAF is also quantifiable and promising, but more data are needed
- Noninvasive models and biomarkers are not quantifiable, with exception of MR-based technology, which is quantifiable and sensitive to change

NASH Diagnosis

- Histological diagnostic criteria: presence of hepatic steatosis, cytologic ballooning, and lobular inflammation
    - No cirrhosis (F4)
- Three different subtypes:
    - NASH without fibrosis
    - NASH with non-advanced fibrosis (stages F1 to F2)
    - NASH with bridging fibrosis or F3
- Comparison of the three histological scoring systems for NASH: NASH-CRN, SAF and Goodman (please see slide #13 in this slide set)
    - NASH-CRN criteria are objective, quantifiable, sensitive to change, have been externally validated, and have been used in clinical trials multiple times
    - SAF and Goodman criteria are similarly objective
    - Limited data re how well they perform over time
    - Not been used in clinical trials;
        - Additional clinical trial data are necessary before they can be recommended for use for regulatory purposes

NASH Non-Invasive Biomarkers (please see slide #14 in this slide set)

- Comparison:
    - Models
        - FIB-4
        - NAFLD fibrosis score
        - FibroMeter NAFLD, etc
    - CK-18
    - Ultrasound
    - VCTE
    - MRI/MRS.
- None of these are able to differentiate NASH from NAFL
- Only MR-based technology is quantifiable. It is able to differentiate various stages of fibrosis with significant degree of certainty, and it is being incorporated into clinical trials now to diagnose fibrosis.
- MR-based technologies appear to be the most promising at this time.

NASH Summary

- NASH cannot be distinguished noninvasively
- NASH CRN criteria is sensitive to change and has been used in clinical trials
- Although the SAF schema is quantifiable, more data is necessary to determine sensitivity to change
- Fibrosis can be quantified via MRE, but more data are necessary
- Similarly, more data from FibroScan and other noninvasive biomarkers are necessary to differentiate between bridging fibrosis and cirrhosis, as well as show change over time in fibrosis stage

NASH with Cirrhosis - Diagnosis

- No definitive test as a gold standard
- Histology may show steatosis or steatohepatitis
    - Histology in itself may not be diagnostic, other than showing presence of cirrhosis or F4 fibrosis
        - Histological features may disappear with progression to cirrhosis
- High degree of clinical suspicion required when the diagnosis cannot be made histologically and the patient has a prior history of nonalcoholic fatty liver disease or features of metabolic syndrome
    - Other competing etiologies of liver disease should be excluded in these patients
- NASH with cirrhosis can be classified as compensated or decompensated
    - based on whether the patient has had a decompensating event
- Some of the characteristic features of metabolic syndrome may start to disappear as patients become more decompensated
    - E.g. a patient with decompensated cirrhosis may not have dyslipidemia due to hepatic synthetic failure as they progress to decompensated cirrhosis
    - Hypertension may improve and the patient may lose significant amount of weight as he or she gets more decompensated
- Good clinical history and prior history of metabolic syndrome is necessary for accurate diagnosis

Noninvasive Biomarkers for NASH with Cirrhosis

- Little guidance on use of noninvasive biomarkers in diagnosing NASH cirrhosis available
    - Most existing biomarker models focus on distinguishing advanced fibrosis from non-advanced fibrosis.
- Unclear how these markers perform in separating bridging fibrosis from compensated cirrhosis from decompensated cirrhosis
- MRE: able to distinguish bridging fibrosis from complex cirrhosis
    - Able to predict clinically significant events before they occur
- HVPG: can predict and follow up portal hypertension
    - no data on the reliability of HVPG in predicting decompensating events in NASH cirrhosis
- Transient elastography needs further validation with regards to the XL probe being able to distinguish bridging fibrosis from cirrhosis and being able to predict decompensating events

NASH with Cirrhosis Summary

- Histology not sufficient for NASH cirrhosis diagnosis
- Biopsy is not always required to make the diagnosis, and clinical suspicion is needed
- MRE and FibroScan can be used to diagnose cirrhosis, but more data are needed
- HVPG can be used to follow portal hypertension in these patients

Gaps in Knowledge (please see slide #19 in this slide set)

- There are two major areas of gaps:
    - noninvasive biomarkers
    - natural history of the disease

- With regard to biomarkers:
    - How well these biomarkers perform as disease changes over time, in terms of grade activity and stage of the disease
    - None of these biomarkers are able to distinguish NASH from NAFLD and more studies are needed to be able to do this accurately
- With regard to the natural history of the disease:
    - true natural history of this disease process
    - how well certain subtypes nonalcoholic fatty liver predict disease progression

Questions, Comments and Discussion:

Q: Regarding steatofibrosis: frequently, biopsies will have significant fibrosis (e.g. septal fibrosis), but no activity (only steatosis). This should be included in the NAFLD group, but as severe disease
Discussion:

- It is indeed difficult to know where to best place steatofibrosis within the paradigm of the three categories discussed. How frequently is it observed? Frequently enough to warrant its own category?
- Difficult to make it a separate category, because it would include some steatosis with very mild fibrosis
    - These would go into the steatosis group
- Steatosis with more advanced fibrosis is the problem
    - Appears to be in 5-10% of biopsies in clinical trials
- An important question going forward as we operationalize definitions for clinical trials and evaluate the resolution of steatohepatitis.
- Two potential scenarios:
    - First: Where we have no fatty liver disease at all (completely cleaned out)
    - Second: No longer have steatohepatitis, but can still have fatty liver
        - Because fibrosis changes over time, may end up with fat and some fibrosis
- Is there a rationale for putting steatofibrosis into the second scenario?
- May have cases where necroinflammatory activity has improved on re-biopsy, but still left with residual fibrosis and some fat
    - Should it categorized differently depending on whether it is observed at beginning of process vs. as resolution?

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        - If seeing as resolution, maybe belongs in first category?
- Given that it is still a minority population, we need to focus on "real" NASH
- Proposal to leave steatofibrosis where it is right now (NAFL)
    - Avoid different set of rules for enrolling patients into trials vs. at end of trial
    - If patients required to have NASH to be enrolled in trials, patients with steatofibrosis would not be eligible in any case

Q: Regarding decompensated cirrhosis: includes cirrhosis without activity, and cirrhosis with active disease, inflammation, ballooning, etc. If these are lumped together, we may miss something important re the prognosis of cirrhosis
Discussion:

- Burned-out NASH with cirrhosis probably behaves differently than cirrhosis with active disease
    - Do we have enough data to determine if one (with active disease) progresses to decompensation faster than the other?
    - If no NASH activity, would patients be eligible into clinical trials?
        - Need to discuss eligibility further?
- FDA perspective: this Working Group needs to come up with a very clear definition of cryptogenic cirrhosis, especially with regard to history of metabolic syndrome
    - What is required with respect to patient history to qualify as cryptogenic cirrhosis secondary to NASH?
    - History of biopsy documented NASH
    - Clear definitions for metabolic syndrome for minimally defined period of years, BMI, and/or diabetes for a certain number of years, requiring treatment?

Q: How do you plan to deal with overlapping ASH and NASH? We're just looking at some degree of overlapping fat content, and that population is probably not that small of a group
Discussion:

- For the purposes of this working group, we're focused strictly on NASH
- Degree of overlap between NASH and moderate alcohol consumption is an emerging field
    - Should collect information on alcohol use in patients enrolled in NASH trials
- Once we have drugs that have shown efficacy, we could assess in secondary studies, see whether the results can be generalized to a broader population
- FDA perspective: Until you have some particularly different drug, you wouldn't mix ASH and NASH until you had proof that you could treat NASH
- Animal studies indicate that the combination of more than just moderate drinking and any kind of diet that induces NASH appears to have a synergistic or at least additive effect

Monitoring and Assessment of Potential Drug Induced Liver Injury in NASH Clinical Trials
Discussion: Is there a need for a NASH DILI WG?
Presenter: Arie Regev, Eli Lilly and Company
Moderator: Arun Sanyal

Please refer to the following slide set:
http://www.hivforum.org/storage/documents/2016/LF4/liver%20forum%204.%20detection%20and%20assessment%20of%20drug%20induced%20liver%20injury%20dili%20in%20nash%20clinical%20trials.pdf

Moderator's Introduction: Drug-induced liver injury is an extremely important subject in drug development in general, and something that everyone is struggling with in the context of chronic liver diseases, where there is already abnormal liver enzymes and evidence of liver dysfunction. We have asked Dr. Regev from Lilly who is involved with collaborative initiatives in DILI to present his perspective of this field and a potential role for the Liver Forum.

- Potential questions and future challenges relevant to NASH drug development that this group should be involved in addressing
  - Is there an increased risk of drug induced liver injury in patients with NASH?
  - What do current guidelines tell us about drug induced liver injury in drug development for NASH?
  - What is the application of Hy's law and how does it relate to NASH patients, and the
    - eDISH for NASH databases
  - With regard to exclusion criteria, how high of an ALT and AST are we accepting in our studies for NASH?
    - What are the implications of accepting higher levels of ALT or AST?
  - Hepatic stopping rules: when do we discontinue treatment?
  - When do we start thinking there is something else going on?

<u>DILI Background</u>

- DILI is the most frequent cause of drug withdrawal from the market in the last 50 years.
  - leading cause of acute liver failure in the United States and Europe
  - exceeds all other causes of acute liver failure combined
    - It is still a major reason for problems with drugs - frequent cause of limiting drug use
- The most significant DILI events in the clinic are idiosyncratic drug induced liver injury
  - specific patients and significant idiosyncrasies of those patients
  - usually unexpected and uncommon.
    - no diagnostic or predictive biomarkers
    - ALT is a sensitive but non-specific marker
- We can, however, predict DILI with careful data collection and analysis during early phases of clinical development.
    - beneficial while we are in the clinical phases of development of a drug for NASH to pay attention to whether this or a similar drug has a record of hepatotoxicity

<u>DILI + NASH</u>

- Are NASH patients susceptible to DILI?
  - We don't know: ongoing debate
  - Lack controlled prospective data
- Prevalent concept among hepatologists that underlying liver disease does not predispose a patient to idiosyncratic drug induced liver injury

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    - Hyman Zimmerman: "The often sighted warning that drugs known to produce hepatic injury should not be given to patients with liver disease has little foundation in fact."
        - Has held the test of the last 20 years pretty well
- Is DILI outcome worse in patients with advanced NASH?
    - Likely
        - low reserve
        - less regenerative capacity, etc
- What do current guidelines teach us about DILI in NASH clinical trials?
    - Most guidelines/published papers address patients with normal livers at baseline (see FDA 2009 guidance)
        - Not much published for patients with underlying liver disease at baseline
    - Addressed differently by different companies
- Patients with NASH comprise an entire group for which we we have no clear guidance on DILI
- How do we diagnose, monitor, and assess potential DILI in a patient that already has an ongoing inflammation due to NASH?

<u>Hy's Law and NASH</u>

- 2009 FDA Guidance: assessment/prediction of hepatotoxicity using Hy's law
    - Need to have all four of
        - ALT and AST of ≥ 3 x ULN
        - Total bilirubin of ≥ 2 x ULN
        - No initial cholestasis (alkaline phosphatase < 2 x ULN)
        - No other cause of liver injury
- Hy's Law – up to 10% risk of liver transplant or death
    - Two cases in 1000 patient trial = increased risk of liver transplant or death in 2/10,000 liver patients = 200 million if drug gets to market

- *Question 1*: Should Hy's Law be applied to NASH patients? *Can* Hy's law be applied to NASH patients with a baseline ALT of ≥ 3 x ULN?
    - NASH patients have "other cause of liver injury"

- eDISH: statistical method used by FDA for every new drug application to assess the potential for hepatotoxicity
    - Representation of the highest ALT and the highest bilirubin level for entire database
        - plot peak ALT vs. peak TBL (see slide 17)
    - Lower left quadrant: normal range
    - Upper right quadrant: Hy's Law range
    - Can click on each point to see patients underlying liver disease (if any)
- Regulatory review: is the drug approvable or not?

- If database includes NASH patients with 3x ULN at baseline?
    - Need discussion and understanding with everyone in the field at the table

- *Question 2*: What ALT level should be an exclusion criterion for NASH trials?

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- Regulatory guidance: If the drug is intended to be prescribed or marketed to such patients after approval, they should be studied during controlled trials
  - If patients with the ALT of 250 intended to be treated in the future, they should be in trial

- Another perspective: is it helpful to enroll a patient with ALT of >200 or >300?
  - Patients with ALT> 300: some other underlying disease?
    - Not typical for NASH
    - May create difficulties later in detecting drug induced liver injury
  - If the patient coming in with 250 jumps to 500:
    - Normal fluctuation?
  - DILI?

- *Question 3*: When should the study drug be discontinued?
  - Current guidelines do not address this question for NASH.
    - Stopping rules apply only given to patients with normal livers at baseline
  - Discontinuing too early will interfere with our ability to differentiate between a bad drug and a good drug
    - a lot of our good drugs may have a mild or moderate increase in ALT, no major safety signal
  - Important to be able to differentiate those patients with mild elevations from those who continue to have a significant liver injury
  - Problematic for NASH patients
    - Previously suggested set of stopping rules:
      - E.g. For ALT 3x baseline or 500 international units
- Example: A patient enters study with ALT of 21
  - Do we stop the study when it rises to 63?
    - Probably not the best time to stop the drug
  - Questions that require some thought
    - May end up stopping many more study patients than we would hope to stop
    - Bad for our studies and we will end up not knowing what the profile is

<u>NASH-DILI Summary</u>

- No clear evidence for increased risk of DILI in NASH patients
  - But DILI outcome worse if in patients with advanced NASH
  - NASH does not protect from DILI
    - Need to monitor for it
- Current regulatory guidance does not address detection, assessment and monitoring of DILI in NASH patients
  - Need to discuss: common understanding of how to handle these issues
  - Hy's law and eDISH may be difficult to apply to all NASH patients especially those with baseline ALT of more than three times upper limit of normal.
    - These are the two main tools that we and FDA use to assess hepatotoxicity
      - The fact that they need adjustment is a critical issue
- ALT and AST exclusion criteria may have important implications in NASH studies

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    - Need to be predetermined
- Hepatic stopping rules may need to be adjusted based on baseline or best pre-event ALT and AST
- Studies of large cross-cohort databases will enable better understanding and improved approaches for detection and assessment of DILI in NASH clinical trials
    - Better soon than later

Baseline Standardization Working Group
Moderators: Joanne Imperial; Quentin Anstee
Presenter:
Claudia Filozof, Covance
Baseline Parameters for NAFLD/NASH Clinical Trials
Draft manuscript prepared by Yuval Patel, Duke University

Please refer to the following slide set:
http://www.hivforum.org/storage/documents/2016/LF4/liver%20forum%204.%20baseline%20parameters%20for%20nafld_nash%20clinical%20trials.pdf

- WG objective: establish a set of baseline parameters to be used in NASH clinical trials
    - consistency and uniformity across trials
        - data comparison/compatibility
    - Uniformity will help the regulatory agencies in their efforts to evaluate safety and efficacy of these compounds
- Reviewed publicly available information on ongoing clinical trials and published studies
    - recommendations for broad categories of data to include in eligibility screening and baseline assessments
    - Considered mode of action, phase of trial
    - Capture essential or ideal

- Broad categories included:
    - Demographics
    - Diet & Activity
    - Anthropometrics
    - Comorbidities
    - Concomitant medication
    - Laboratory tests
    - Liver histology
    - Health related quality of life
    - Potential non-invasive diagnostic tools

Demographics
- Gender, Age, Race, Ethnicity
    - NAFLD is more prevalent in males relative to females
    - Gender differences in terms of insulin resistance, modified distribution, and potential complications

    - Impact of age on liver fibrosis progression in mitochondrial dysfunction, and comorbidities (e.g. CVD) s
- All Essential for phase 3
    - Gender: Essential POC or phase 2b
    - Age: Essential POC or phase 2b
    - Race: Ideal for POCor phase 2b
    - Ethnicity: Ideal for POC or phase 2b

Diet and Activity (including alcohol, smoking and substance use)

- Recommend that all patients be counselled to adopt a "generally healthy diet" with easy compliance evaluation
    - Avoid major changes in diet and activity during trial follow-up
    - ADA guidelines for diabetic patients
    - NCTP guidelines for non-diabetics or any equivalent in the different countries
    - Recommend that the period between the screening visit and the baseline visit be used to standardize lifestyle advice and counseling
- Evidence suggests that dietary changes have no impact in NASH specific outcomes
    - Dietary changes may affect liver fat and ALT levels
    - Weight loss may lead to histological changes
- Recommend short version of the IPAQ tool assessment of physical activity (essential)
- Assess alcohol consumption in all trial phases (essential)
    - Recommend use of the AUDIT, AUDIT-C or the NIAAA
    - The AUDIT-C has only two questions, recommended as essential
    - Complement with phosphatidylethanol assessment

- Smoking habits (if not exlusion criterion) essential in all trials
    - Some data suggest smoking may influence progression of NASH
    - Impact of smoking in impairing insulin sensitivity

Anthropometric measurements:

- Careful characterization of phenotype can be useful in identifying factors influencing response to treatment
- Weight, BMI, Waist Circumference and Blood Pressure
    - Essential for all trial phases
    - Consider other circumferences

Comorbidities and other liver diseases

- Includes type 2 diabetes, hypertension, hyperlipidemia, cardiovascular disease, obstructive sleep apnea, autoimmune disease, obesity and history of weight loss/bariatric surgery
- Essential to capture across all trials
- Some should be exclusion criteria
    - Other chronic liver diseases, history of DILI, alcoholic liver disease, Wilson's disease, genetic hemochromatosis, known or suspected HCC, Gilbert's disease, depression

- Specific comorbidities may have an impact on drug clearance or tolerability and the safety of the compound.
- Renal function affects drug clearance and metabolism

Concomitant medications

- Essential to capture:
  - Antidiabetics
  - Vitamin E
  - PUFA/W3FA
  - Ursodeoxycholic acid
  - Statins and fibrates
  - Antihypertensives
- Pay special attention to drugs that can have a positive or negative impact on NASH parameters

Laboratory Tests

- Metabolic Profile: Essential for all trial phases
  - Fasting blood glucose, insulin, and hemoglobin A1c are essential for both early and late phases of trial close association between diabetes and NASH,
- Lipid profile essentials
  - total cholesterol, and diffractions, and triglycerides
- Hematology, liver panel and blood chemistry: Essential for all phases
  - ALT, AST, ALP, total bilirugin, GGT, albunin, prothrombin time/INR, hemoglobin, hematocrit, platelets, BUN, creatinine
    - important from the safety perspective
    - key markers of liver function.

Liver histology

- Histological confirmation of NASH essential for Phase 2B and Phase 3 trials
  - Ideal for proof of concept/phase 2A trials
- Recommend NASH-CRN scoring system, including the NAS and fibrosis stage
  - The SAF score can be included in addition to the NAS score
    - Gather more data about SAF in trials

Specialized biomarkers

- Await validation of non-invasive biomarkers before recommending for baseline assessment
- Take opportunity offered by new clinical trials to accelerate investigation and validate biomarkers
- Specialized biomarkers: role in confirming mechanism of actions or for PK or PD purposes

Genetic markers (see slide #19)

- Selected genetic polymorphisms are associated with liver disease severity and with cardiovascular disease
  - PNPLA3 and TM6SF2 are known markers of NASH
- Recommend PNPLA3 as essential in Phase 3 trials
  - can help identify patients metabolic NASH

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    - may eventually predict differences in response to treatment
- Essential to storing DNA for future genetic analysis
    - Obtain appropriate informed consent

Imaging

- Available imaging methodologies to assess liver stiffness have several limitations
- MRI or MRS essential for early phase studies with changes in liver fat as primary endpoint in patients without histological confirmation of NASH
- Imaging can be used early phase trials to enrich a population, without histologic confirmation
    - Not applicable in phase 3 trials
- Some variations of MRI (e.g. multiparametric MRI) provide information about inflammation and fibrosis in addition to liver fat
    - Need further validation
- Fibroscan and other the non-invasive biomarkers can also be helpful to enrich populations (phase 3) or in phase 4 in patients that progress to fibrosis.

Health-related quality of life

- Recommend the use of either the SF-36 or the Specific Chronic Liver Disease Questionnaire as essential in Phase 3 trials
- Not applicable for short POC trials
- Ideal for longer proof of concept or Phase 2B trials with at least 52 weeks of follow up

Questions, Comments and Discussion

Moderator: The working group is still developing a list of concomitant medications and also refining the recommendations with respect to diet, exercise, and alcohol consumption

Q: Regarding the recommendations that no major alterations in diet and exercise should be undertaken by patients: How should counseling on dietary measures, lifestyle in general, be included into standard of care? How can you prevent a patient from engaging into a healthy lifestyle within the clinical trial? Would this pose ethical problems if you prevent them?
Discussion:

- We recommend counselling for adopting a healthy diet and lifestyle during the period between screening and baseline, and then discouraging major changes during the trial to avoid any impact of those changes on response to treatment
- It is important to counsel patients to meet ethical standards without making an intervention out of it, because then it becomes an artificial construct. Good counseling regarding general lifestyle is part of normal patient care

Comment: We should not be too prescriptive about genetic testing. It is a good idea to collect the material, but beyond PNPLA3, there may be drug specific genetic polymorphisms that may be relevant.
Discussion

- Discussed at length by the working group. PNPLA3 is the poster child for genetics And so it's the one that everyone reaches to particularly in Phase 2

- Going beyond that, we need to have a consent in place for genome-wide scans because it is relevant to drug induced liver injury and various other scopes. So while, we recommend PNPLA3 as essential here, the ideal would be to move towards a genome-wide approach

Comment: A couple of semantic points regarding the term MRI Proton density fat fraction/MRS.

- Can measure fat using MRS, correctly or incorrectly
- Can measure fat using MRI, correctly or incorrectly
- Proton density fat fraction is the most correct measure of fat, and it can be measured either with MRI or MRS
- The advantage of MRI is that it sees the entire liver and especially in the longitudinal trial, can make sure that the regions of interest are spatially co-localized
    - any change in the measurement from time point one to time point two represents a real change and not just a sampling variability issue
- At this time (2016) it is not possible to measure proton density fat fraction with MRI or MRS if the trial has 10 sites or more
    - need to partner with someone who can help come up with the best least common denominator that minimizes its many confounding variables
- MRE, done properly, is probably right now the most accurate way non-invasively of measuring stiffness in the liver
    - has to be done properly -- not in widespread use throughout the world
        - Will need to be a training phase if implementing MRE at different sites
- Word of caution about ultrasound elastography
    - Vibration controlled transient elastography is very robust
        - reliability of some of the newer devices has not yet been proven
    - Using ultrasound elastography devices at different sites from different manufacturers requires extra caution

Q: Has any consideration been made regarding the use of herbals, homeopathic remedies, marijuana and other drugs by patients? Also, have you considered collecting information about income level and geographic location?
Discussion:

- Not discussed yet, but a very important point that needs to be addressed

Pediatric Issues Working Group
Presentation of Working Group draft manuscript on pediatric definitions and baseline parameters),
Followed by
General Discussion
NEXT STEPS: Framework for Pediatric Natural History Cohort Transatlantic
Moderators:
Joel Lavine, Columbia University Medical Center
Miriam Vos, Emory University School of Medicine

Please refer to the following slide set for this presentation;
http://www.hivforum.org/storage/documents/2016/LF4/liver%20forum%204_pediatric%20wg.pdf

Introduction to the Pediatric Issues Working Group

Moderators' Introduction: Definitions and baseline parameters: in many cases these intersect with what was discussed already with adults; in many cases, there are areas of difference
The working group has developed a document summarizing the current state of affairs on regulatory considerations for clinical trials in pediatric populations. We are in the last stages of refinement, so the document should be ready in advance of the next meeting

- Why is pediatric fatty liver disease important?
    - Pediatric obesity has increased threefold to become the most common pediatric liver disease in last three decades
    - Health disparity insofar as certain ethnic groups are particularly predisposed in the United States: Hispanics, indigenous Americans, and Mexican-Americans
- Many of these children develop significant disease at a very young age
    - cirrhosis as early as eight
- These patients either have a genetic predisposition or environmental susceptibilities that exceed what might be found in adults
- If they have other comorbid conditions causing liver disease, there are combinatorial additive or synergistic effects
- Treatment options are limited, as in adults

Definition of NAFLD in children is not different from that in adults

- ≥5% percent of the hepatocytes demonstrating macrovesicular steatosis, which can be mixed with microvesicular steatoses
- Lack of significant ethanol ingestion, while not so important in younger kids, may become significant as they become adolescents
- No other identifiable causes of fatty liver
- Exclude Hepatitis C, inborn metabolic errors such as carnitine deficiency or inborn errors of fatty acid synthesis, autoimmune hepatitis, Wilson's disease, et cetera

Histological differences from adult disease.

- Approximately ¼ to 1/3 of pediatric patients have a unique pediatric pattern, called Type 2
    - Pronounced ballooning and perisinusoidal fibrosis – rare in adults
        - NASH CRN calls it a borderline zone 1 pattern
- Kids also get the adult type, called Type 1
- Pediatric pattern associated with significant pathology resulting from more portal fibrosis and generally more portal inflammation

Pediatric disease in the context of drug development.

- Both the EMA and the FDA mandate pediatric programs
    - U.S. : Pediatric Research Equity Act (PREA)
    - requires sponsors to have a pediatric study plan developed and approved prior to adult drug registration

Controlled trials in children

- Two large-phased randomized controlled trials in children completed
  - TONIC: metformine vs. vitamin E vs. placebo
    - primary endpoint: ALT reduction
    - secondary endpoint: NAS reduction ≥2 with no worsening of fibrosis
    - Placebo group had lifestyle intervention provided as standard of care
- CyNCH:
  - Primary (histologic) endpoint: NAS reduction of 2
    - completed last year and manuscripts under review for publication
  - First study to use extensive histology in the primary outcome measure

Inclusion criteria considerations

- Age and size
  - Children need to be old enough to swallow pills reliably
  - Clinical differences between 8-year-olds and a 17-year-olds
    - prepubertal versus peri and postpubertal differences in hormones – estrogen and testosterone - affect lipid metabolism, inflammation, and fibrosis
  - In terms of the size, the pill dosage makes a difference
- Consider whether alternative approaches have been tried, including lifestyle alterations and Vitamin E treatment
- Severity of disease features
- Ascertaining the diagnosis
  - Has been based on liver biopsies
  - Non-invasive methods are only now being considered

Trial considerations

- Benefit/risk of the drug compared to the natural history of fatty liver disease in children, given the natural history is in large part undescribed
  - NASH CRN conducting natural history studies that will yield data useful to evaluate risks of side effects and complications versus the potential benefit
- Dose adjustment based on size
- Pill form versus liquid and how that relates to compliance
  - drug administered by parents or self-administered?
  - Consider child moving from home at 18 or 19 and potential for drop-out
- Informed consent: Assent from the older child needed as well as consent from a parent
- Fear of procedures
  - younger children
- Recruitment difficulties due to the requirement of a second end of treatment biopsy
  - In the two randomized clinical trials described above 85% of of patients did undergo the biopsy at the end without coercion

Non-invasive surrogate endpoints in pediatric trials

- Potential noninvasive methods

    - E.g. MR: can quantify fat,visualize the entire liver
    - Can see the fibrosis where fat is missing, replaced by scar
- Imaging modalities not yet validated
    - maybe useful in near future in the context anti-fibrotic trials

Unmet needs in pediatric NASH

- Imaging modalities not yet validated
    - maybe useful in near future in the context anti-fibrotic trials
- Noninvasive modalities that would allow us conduct trials without a research biopsy
- avoid a standard of care biopsy?
- Noninvasive means of monitoring progression and likelihood of a treatment response
- Effective therapies
- No more than 50% of trial patients meet the primary outcome endpoints
- generally histology-based
- None of these are based on clinical outcomes
- Direction from the FDA on registration qualifications so that manufacturers/developers of existing drugs and drugs in development could know with some assuredness that they are looking at the right criteria to qualify if they indeed meet the bar set

NASH Ideal Therapeutic

- Safe and well-tolerated
- Efficacious for the majority—better than 50%
- Combinations of targets and comprise combinations of drugs
- Oral, once a day
    - or infrequent injection
- Affordable
- Would address other metabolic syndrome comorbidities
    - e.g. dyslipidemia, insulin resistance, obesity

Proper Registrational Endpoint Considerations

- Reduction of NAS score of two or more points with no progression of fibrosis
- Co-primary endpoints that are often included in adult trials, including resolution of NASH with no worsening of fibrosis, regression of fibrosis with no worsening of NASH and diminution in hepatic venous pressure gradient
- Endpoints that match both a type 1 and a type 2 NASH or which allow for the separate analysis of results from each type

Gaps in knowledge

- Predictors of short and long-term clinical outcomes
- The effect of resolution/non-resolution of NAFLD on the risk of type 2 diabetes and cardiovascular disease
- Validated surrogate endpoints

Proposal for Pediatric Natural History Framework

- The purpose of such a framework is to weigh benefit/risk of treatments and to know how the type 2 NASH pattern evolves
- Pediatric patients are the most genetically and environmentally susceptible people
    - Does it have a different natural history?
    - Does it have differential treatment responses?
        - how it is/is not affected by other risk factors, such as heavy alcohol use?
    - Don't know the outcomes of pediatric disease in young adults
- Transatlantic, collaborative natural history studies
    - allow for data sharing so that every company isn't left on its own
        - best course for at-risk populations throughout the world
- Studies that roll into longitudinal cohorts is one way to accomplish this
- DNA samples should be obtained to be able to later determine the factors most responsible for why they acquire this disease so early
- Lose data when children transition from pediatric care
    - often they see no doctor at all during young adulthood
        - need mechanisms to follow what happens to them once they transition out of pediatric care
- Recommendations regarding data that should be collected uniformly across pediatric studies
    - age
    - pubertal status
    - gender
    - boys outnumber girls in pediatric NASH about 2.5 to 1, when adjusted for degree of obesity
    - visceral adiposity versus peripheral adiposity
    - race and ethnicity
    - weight, height, BMI z-score
    - waist circumference
    - metabolic syndrome comorbidities
    - family history of liver disease
    - other medications
    - other systemic diseases
    - grade and fibrosis stage in the NASH type

Next Steps

- Convene a pediatric natural history working group
- Complete and release the pediatric document specifying definitions and baseline parameters for pediatric NASH trials
- Develop a plan for a longitudinal follow-up study of pediatric trial patients
- Develop a plan for a pediatric natural history study

Final thoughts: Pediatric NASH is a problem that is recognized now in the basic science literature

- Feature story in *Science* from last summer about "The Liver's Weighty Problem,"
    - Covers pediatric NASH

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- NASH is named as one of the greatest looming problems of the 21st Century by *Newsweek Magazine*.
- It's on the front page of *The New York Times*.
- We are the right people to be addressing a big problem at the right time

Questions, Comments and Discussion

Comments/questions:

- The importance of getting input into pediatric document from the entire LF
- Getting regulatory input into the pediatric guidelines—from both the EMA and FDA
- Harmonization efforts between the EMA and FDA with regard to pediatric trials
- Harmonizing pediatric and adult criteria, to the extent possible

Discussion

- The pediatric development programs and their assessment are not essentially different between the FDA and EMA
    - The only obvious difference is the requirement earlier submission in Europe than for the FDA
- FDA has a meeting planned with EMA Pediatric Group
- The FDA has not finalized criteria for adults, but is tending towards recommending that inclusion criteria for trials be restricted to NASH patients with fibrosis ≥ F2, and maybe F1 with high risk factors
- Inn children we may need to have a broader population because they're starting earlier
- It is concerning that they have more aggressive disease
- But without the natural history data, we're just extrapolating from adult data to children without knowing if that is right

Q: Affordability is an important characteristic for effective therapy. Could that concept be expanded to include equity, to facilitate distribution of effective therapies to all populations in need?

Q: Are the figures of obese children emblematic of what is seen in pediatric NASH? Really high BMI's? Are there other kids with "lean NASH" or leaner NASH that we see there?

Discussion:

- Drawing from the CyNCH or TONIC patient populations, the average age is 13 years old and generally 70 percent are boys
    - Around 95% are obese
    - 4% are overweight
    - Just a small fraction are lean/normal body weigh
    - The average waist circumference, is about 104 centimeters
    - Their average BMI is usually 32, unadjusted for age
    - BMI-z-score is around 2.5
    - The remaining 4 percent or more are overweight. Just a very small fraction of these patients are lean or normal body weight
- Clinically we see a bigger range than what was seen in the trial

- Varies by race and ethnicity

- Selection bias regarding who comes to clinic and gets biopsied
- How do they get recognized as having this in the first place?
  - Our first patients were identified when, upon entering 7th grade, they came in to get a PPD for tuberculosis
    - Many living along the Mexican-American border have positive PPD
      - put on isoniazid=hepatotoxic drug
      - LFTs checked; really high ALTs – (125-150 range)
    - Referred if LFTs high on re-test
- Recognizing the high risk population community health centers and general pediatricians in community started screening and referri ng
- Probably different reasons for why people come in in different centers across the US
  - almost always starts out with that they are heavy and have a high ALT

Q: If the children are histologically different from adults, why do we think that the same drugs that would treat adult NASH will or will not address this disease in kids?
Discussion:

- Well, we don't know
- That is why we need clinical trials in children rather than just extrapolating what dose you need for a child after a drug is approved for adults

Q: If 10% of the TONIC placebo group patients develop diabetes, would that be considered a clinical outcome in a natural history study of suspected fatty liver disease in children or confirmed fatty liver disease in children?
Discussion:

- Would likely be a safety endpoint
- Need to have secondary endpoints looking at cardiovascular and metabolic outcomes because we don't want to save the liver and kill the person

Q: Holding off on pediatric treatment trials until we have more natural history data raises the issue of whether we will be able to obtain adequate numbers for placebo controlled trials
Discussion:

- Not all pediatric NASH trials should necessarily be held off
- In children, we need to have proof of a prospective direct benefit
- Unless it is an immediately life-threatening disease, generally obtain proof in adults first
- Relevance of nonclinical data
  - Can use nonclinical data or juvenile animal models
- Can use adult studies to provide sufficient proof of prospective direct benefit to initiate a pediatric trial
- A placebo control trial, even in children, is the right thing to do if that is the only way to obtain a real answer

Q: What is the approach if a sponsor does not know enough to submit a PIP, including what enpoints would be used?
Discussion:

- It is very reasonable to submit one saying, "We don't have all the data here. These are gaps in knowledge. We know we need to gather more natural history and we're working on that."
    - Include a general outline of your plan for pediatric formulations and a general estimated time when the sponsor will have proof of prospective direct benefit, because if that's based on the adult studies, some results should be available. In other words, a very general submission

Q: Recruitment -- has the working group considered the situation in pediatric type 2 diabetes? There are a number of ongoing trials, but they are not able to recruit patients. We could be looking at the same situation in pediatric NASH, where we will have a number of trials but find that it is difficult to recruit patients into those trials.
Discussion:

- Yes, that is a potential problem in the very near future with adults in NASH and in pediatrics
- That is why the Liver Forum engaged in the work on data standardization, to facilitate centers that run multiple drugs with one placebo group
    - With one placebo group, we have fewer patients on placebo and more patients available to try different new drugs
        - If we can standardize the trials, we can do that

Q: Regarding biopsies in children

- Why would we be allowed to do a research biopsy on a child who's on a placebo?
    - If there is more than minimal risk to a child, there has to be the potential for benefit
- Why conduct biopsies on children as standard of care?
    - we need to exclude something else causing disease
    - have found autoimmune hepatitis by doing a biopsy for what was thought to be NAFLD
- If NASH is diagnosed, vitamin E is recommended
    - That doesn't apply if they didn't have a biopsy and you don't know they have NASH

Q: Could vitamin E be used in lieu of placebo in pediatric trials?
Discussion:

- Vitamin E has not been shown to improve fibrosis
- We know fibrosis is a good surrogate for disease progression, so while vitamin E reduces the acute inflammatory response -- it's possible that we didn't follow the patients long enough to get a fibrosis readout
    - Some evidence in adults, that resolving steatohepatitis, leads to improvement in fibrosis.
- Cannot justify putting vitamin E into every trial

- If vitamin E were considered standard of care, we wouldn't be testing a drug against vitamin E
    - Everyone would receive vitamin E, with the new drug as an add-on

Q: An analogous trial design issue pertains to hepatitis C. With SVR, there is a biological possibility that the liver disease will improve, that the patient will longer and won't have liver-related outcomes. Can we think of a way to take people who in the short-term show some sort of histologic response forward for the long-term analysis?
Discussion

- The issue gets complicated because for that we need a placebo arm
    - can't cherry-pick in one arm and not the other
- Maybe we need to engage in a discussion about looking for changes in resolution of steatohepatitis with or without some degree of fibrosis improvement, after the intermediate histologic endpoint has been met.
    - Can we refine the population that goes forward for the long-term part of the study?

Next steps

- Form a working group on the natural history of pediatric disease
    - Those interested in participating in that, please send an email to the Liver Forum
- In pediatrics we have a lot of similar issues compared to adults yet we do have enough differences that the pediatric trials are going to need to go forward
- Even though we are raising many issues, we need to recognize the positive
    - several large clinical trials have been successfully completed in children with biopsies
- We have made a lot of progress
    - working on the details of the next trials
- It will continue to be a work in progress

Mapping Potential Placebo Arm Cohort
Clinical Trials Review
Presenters: Veronica Miller (summary of work by Lauren Smith)

Please refer to the following slide set:
http://www.hivforum.org/storage/documents/2016/LF4/liver%20forum%204.%20mapping%20potential%20placebo%20arm%20cohort%20.pdf

Background in terms of the kinds of data all of the sponsors are generating and that if we proceed with collaborations in this area we would have available

- Review of characteristics of placebo arm patients from NAFLD/NASH clinical trials registered with clinicaltrials.gov
    - Recently initiated, Phase 2, 3, or 4, placebo controlled, interventional trials studying drugs or biologicals on the regulatory pathway investigating primary liver endpoints
- 25 trials met basic criteria for inclusion in the review
    - 22 are phase 2 trials
- Number of sponsors enrolling patients in each stage of disease
    - The majority of the trial patients are in the later stages of NASH

- Estimated number of placebo arm patients from the 25 trials
    - Approximately 1,760 patients

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        - Majority in NASH with early and advanced fibrosis

- Entry diagnostics
    - 19/25 trials required baseline liver biopsy
    - 6/25 conducing liver imaging at baseline
    - 2/25 required either imaging or biopsy

- Seven publications available
    - enrolled 404 placebo arm patients
        - average age: 51
        - Sex: 40% male
        - ALT/AST: 73/51
        - AK: 78.5
        - Fasting insuling: 154
        - BMI: 32.9
- Time between baseline biopsy and study entry: 3-18 months
    - Majority: 6 months

Special Presentation:
Making the Most of Data: Targeted Learning and Potential Applications
Mark van der Laan, UC Berkeley

Special Presentation:
Innovation in Data Collection
Trang Gisler, My Own Med

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