“Van Nonalcoholic Fatty Liver Disease (NAFLD) naar Metabolic (dysfunction) Associated Fatty Liver Disease (MAFLD): een update”

Het standpunt van de regelgevende instanties ivm MAFLD: diagnose en eindpunten

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Disclaimer

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Regulatory Decision Making

Benefit Risk Uncertainty



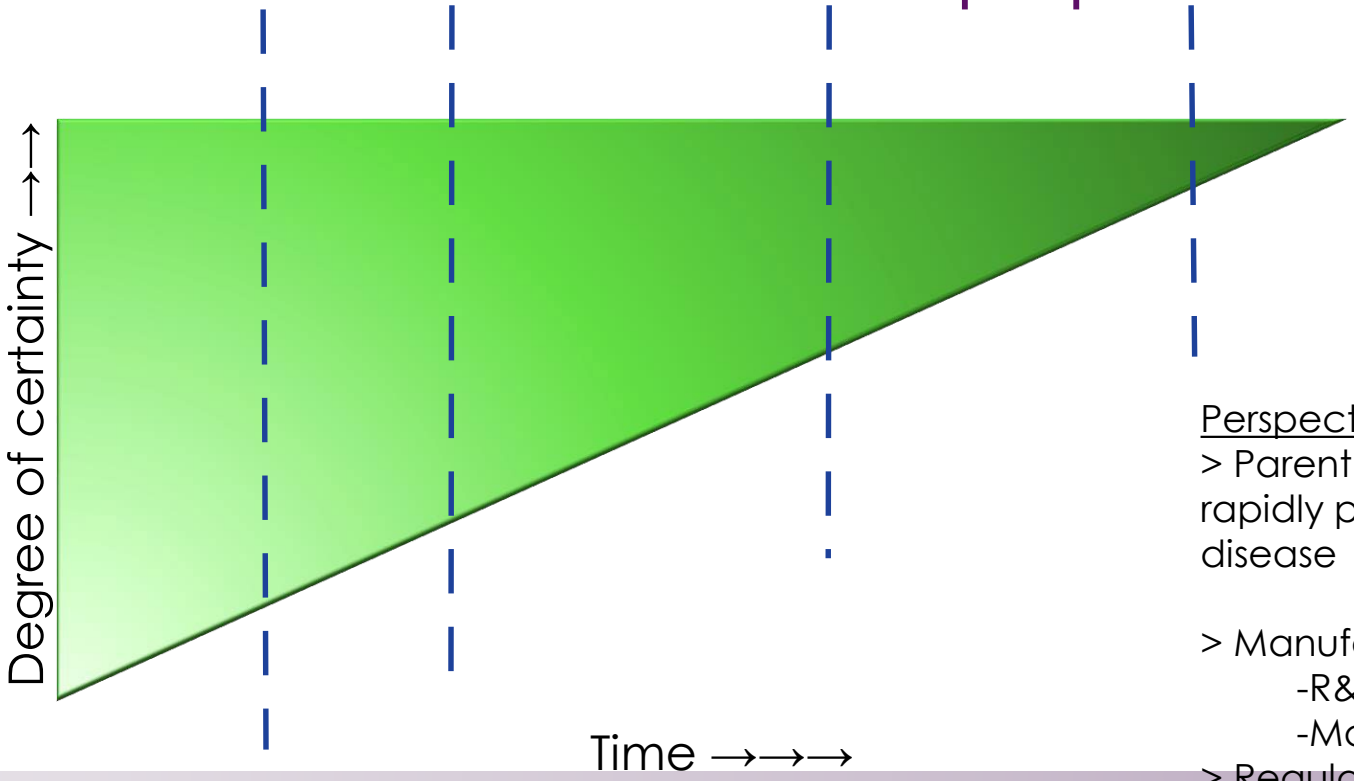


Regulatory Decision Making

- Benefit→ How much is enough?
- Risk→ How much is too much?
- Uncertainty → How much can we live with?

Who decides?

Woodcock: “Drug development can be described as the progressive reduction of uncertainty about the effects of a molecule in people”



Perspectives

> Parent of a child with rapidly progressing rare disease

> Manufacturer
- -R&D
- -Marketing

> Regulator

Not an easy task

FDA increasingly approves drugs without conclusive proof they work

Health Jun 26, 2018 11:31 AM EST

“I would say to a patient, this drug may be more likely to shrink a tumor either partially or even completely, but that may in fact be a pyrrhic victory if it doesn’t help you live better or longer.”

“Clearly, accelerated approval has greater uncertainty.”

https://www.pbs.org/newshour/health/fda-increasingly-approves-drugs-without-conclusive-proof-they-work



Not an easy task

- Expediting drug development for serious illness: Trade off between patient acces and uncertainty

Janet Woodcock

Clinical Trials
2018, Vol. 15(3) 230–234

EMA Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases

Recognizes difficulty in assessing hard clinical outcomes and dependence on liver biopsy

Patient populations:

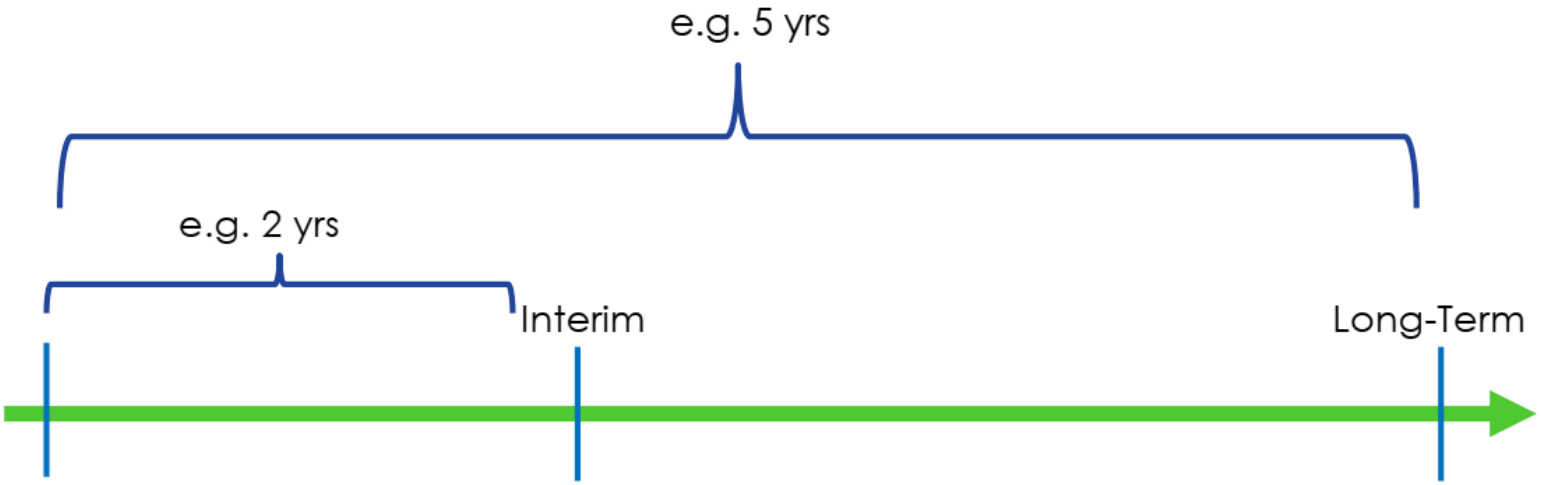
Cirrhotic/non-Cirrhotic

EMA: non-cirrhotic patients

Exclude F1 (low risk of progression)

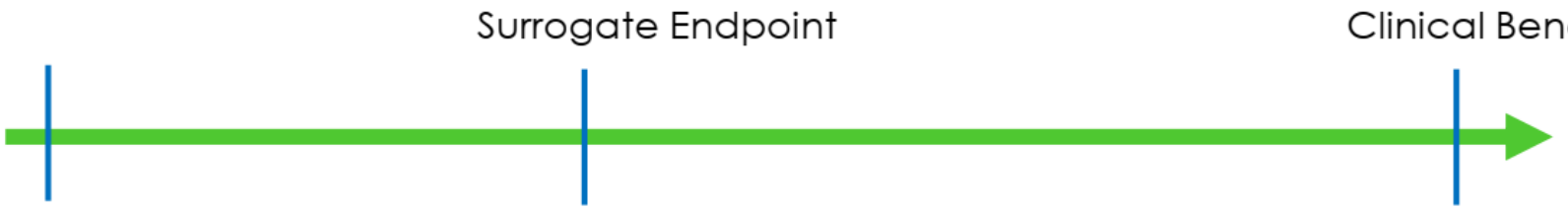
The natural long-term endpoint in clinical trials for NASH would the combination of all-cause mortality, livertransplantation and the manifestations of decompensation (variceal bleeding, ascites, encephalopathy etc.)

Natural endpoint may be unfeasible
EMA non-cirrhotic





Natural endpoint may be unfeasible
FDA non-cirrhotic





Cirrhotic Patients

EMA

- Long term strategy
  - All cause death
  - Decomp events
- Possible interm strategy
  - F4 > F3?
  - Lowering MELD
  - Lowering HVPG

FDA

- Traditional approval
- Time to first event
  - Ascites complications
  - Variceal hemorrhage
  - Hepatic encephalopathy
  - MELD $\geq$ 15
  - Liver transplant
  - All cause mortality

The Patient Voice is Not a Chorus!

