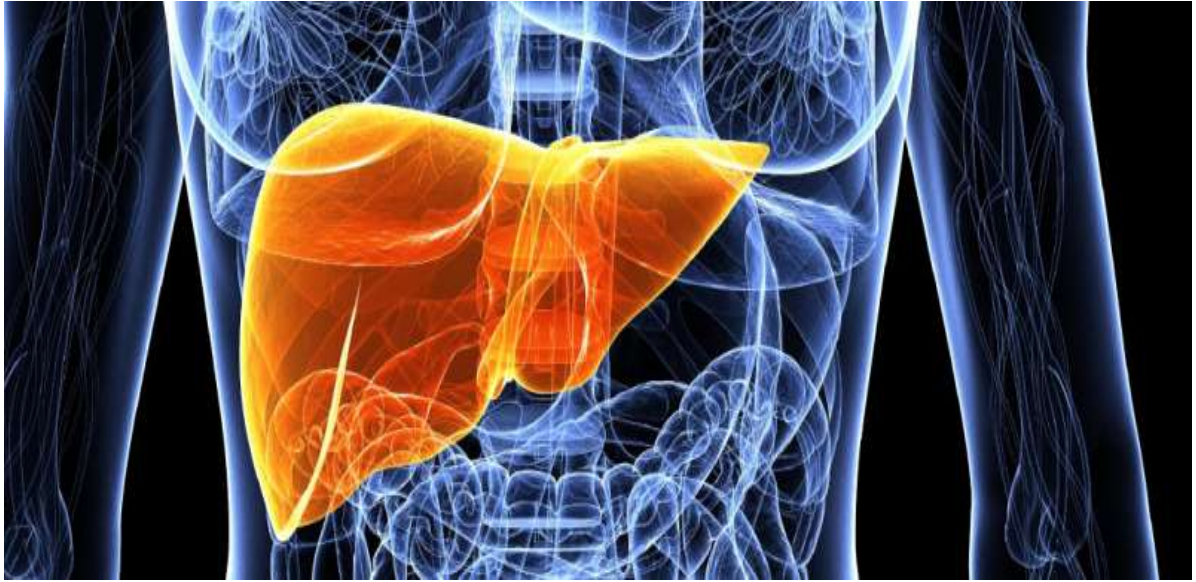
DAx/TM



LIK066, an SGLT1/2 inhibitor for the treatment of NASH

Chinweike Ukomadu MD, PhD
Disease Area X And Translational Medicine
Novartis Institutes for BioMedical Research
NASH-TAG 2018

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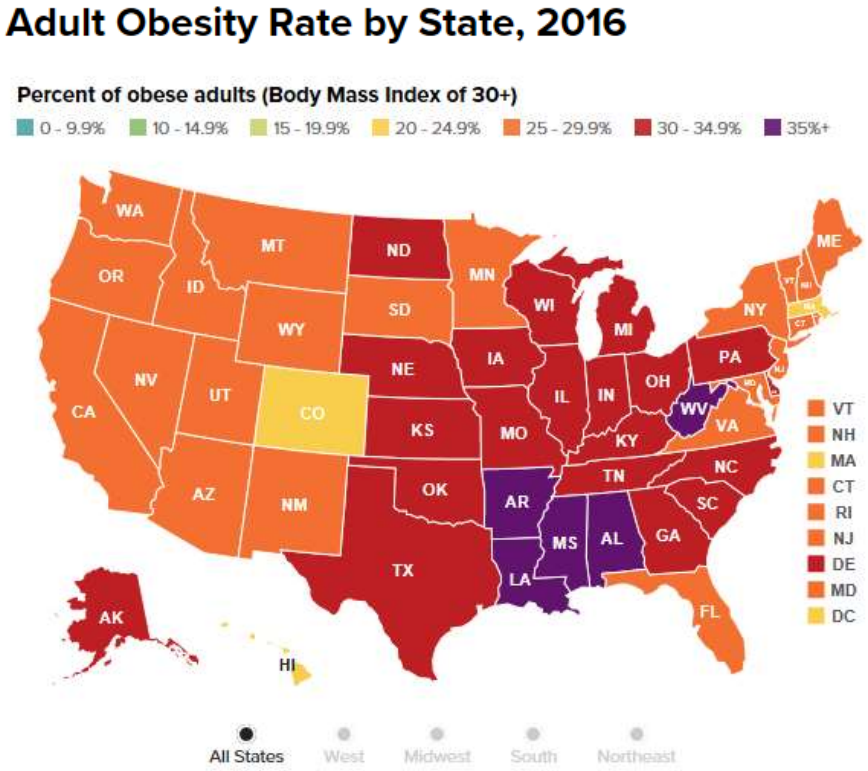
NASH: A global health crisis in the making



- Prevalence of NASH is increasing with rising prevalence of obesity
- NASH is expected to be the leading cause of liver transplantation by 2020
- ~65 million with NAFLD now, 100 million by 2030
- 16.5 million now with NASH, 27 million by 2030

Wree et al, ***Nat. Rev. Gastroenterol. Hepatol***. 2013
Estes et al, ***Hepatology*** 2017

http://healthyamericans.org/reports/stateofobesity2017/

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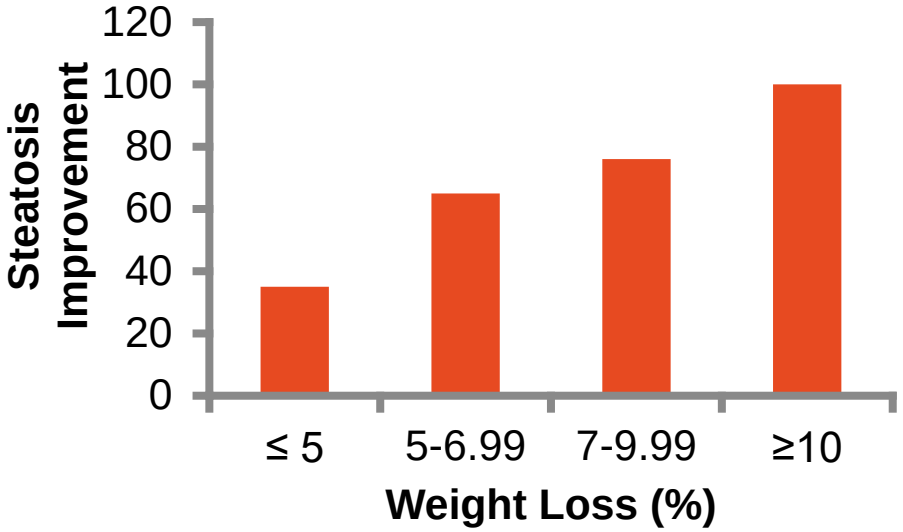
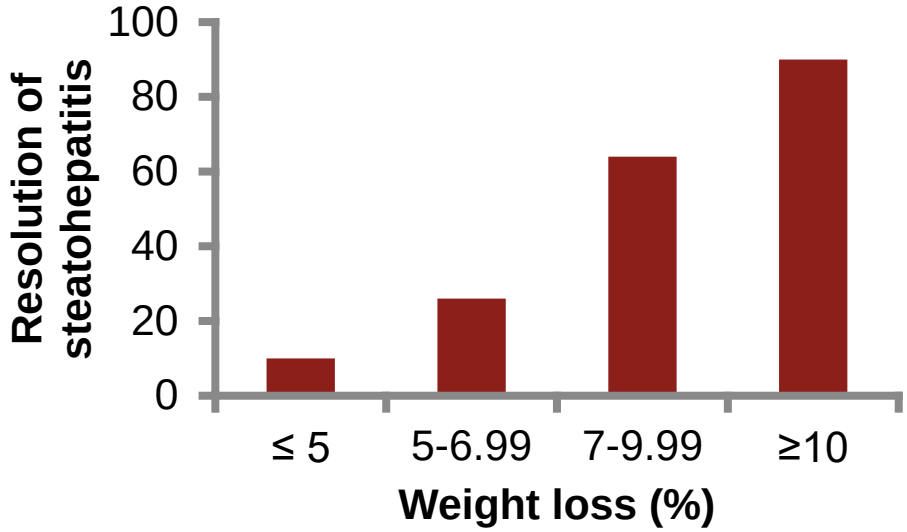
Weight loss improves NASH histology after 52 weeks of lifestyle modification



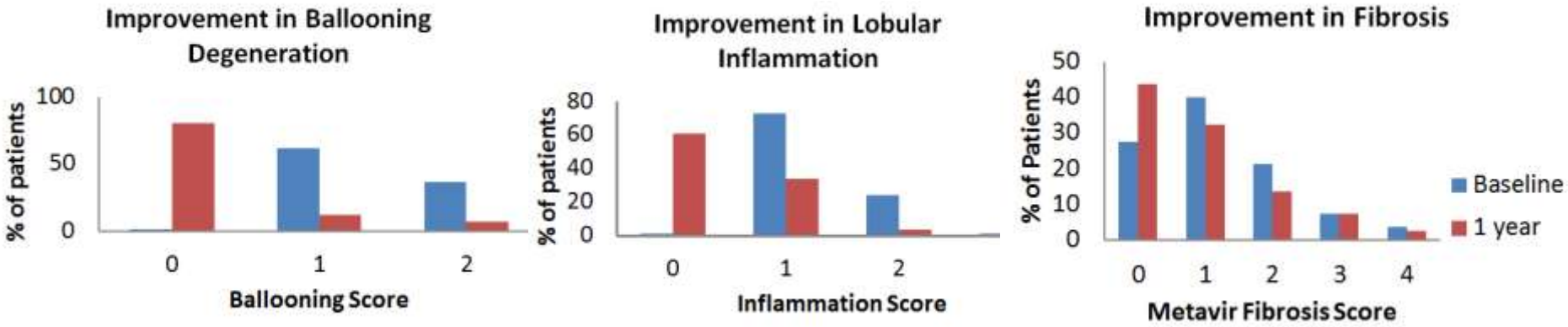


- 5% weight loss improved steatosis
- 7% weight loss improved hepatocellular ballooning
- 10% weight loss needed for fibrosis improvement

Vilar-Gomez E, et al. ***Gastroenterology*** 2015

Bariatric surgery improves histologic NASH

Bariatric surgery improves histology after 1 year



- All aspects of histologic NASH improved
- ALT and insulin resistance improved
- Patients without improvement of NASH had lower weight loss

Lassailly, et al. ***Gastroenterology*** 2015

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Therapies that impact co-morbidities associated with NASH will be essential

- Obesity, T2D and metabolic syndrome are associated with NASH
- Liver related death is not the leading cause of death in NASH*
  - Cardiovascular
  - Non-liver cancer
  - Cirrhosis complication
  - HCC
- Therapies that decrease body weight, improve insulin resistance and potentially decrease lipotoxicity should have favorable impact on NASH
  - An SGLT1/2 inhibitor is expected to affect multiple aspects of NASH

*Angulo et al, ***Gastroenterology*** 2015

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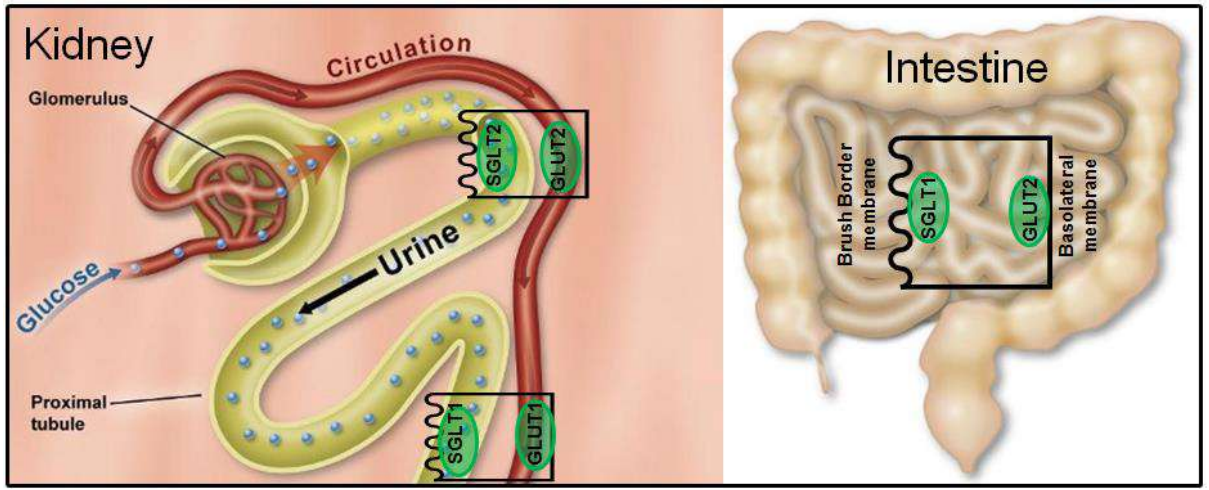
Effects of SGLT1/2 in kidney and gut

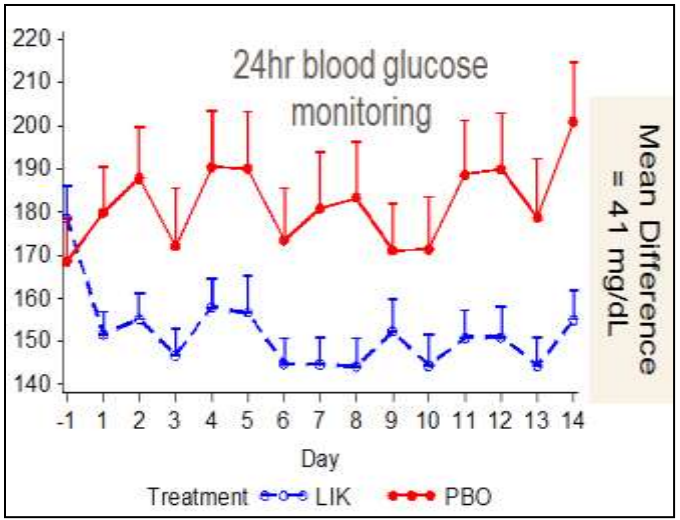


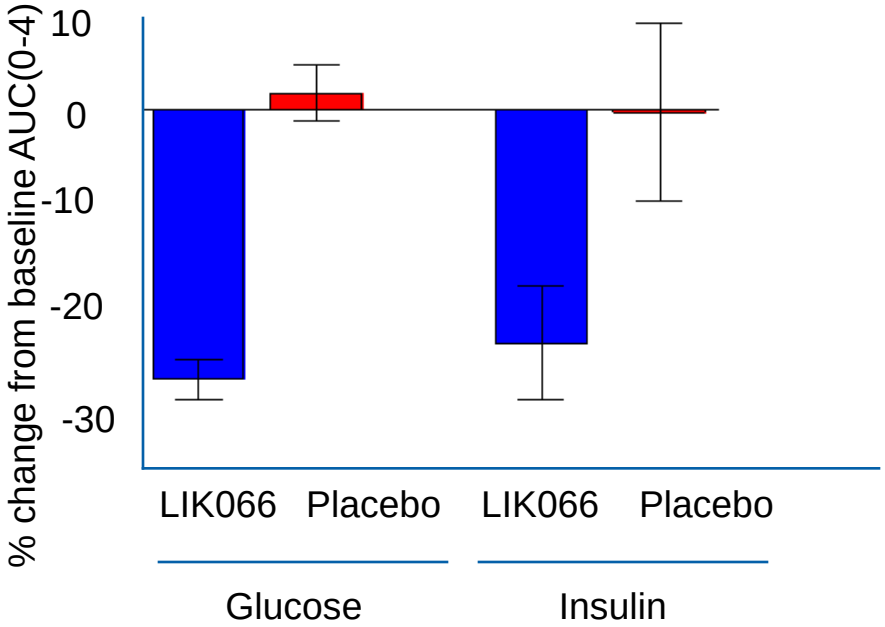
LIK066 blocks absorption of filtered glucose by ***SGLT1 and SGLT2 in the kidney***, resulting in increased loss of glucose through the urine over SGLT2i

LIK066 also inhibits **intestinal SGLT1** which delays intestinal glucose absorption and stimulates distal L and K cells to release incretin hormones which modulate insulin action.

LIK066 should produce superior glycemic control compared to selective SGLT2 inhibition through combined renal and gut effects

LIK066 improves blood glucose in diabetic patients





- LIK066 also increases post meal levels of GLP-1 in T2D patients

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LIK066 improves multiple metabolic parameters in dysglycemic patients over 12 weeks

Variable	Change
Body Weight	-6.83 %
Waist Circumference	-6.95 cm
HbA1c	-0.43 %
Fasting Glucose	-14.5 mg/dL

- Placebo-subtracted change from baseline at 12 weeks.

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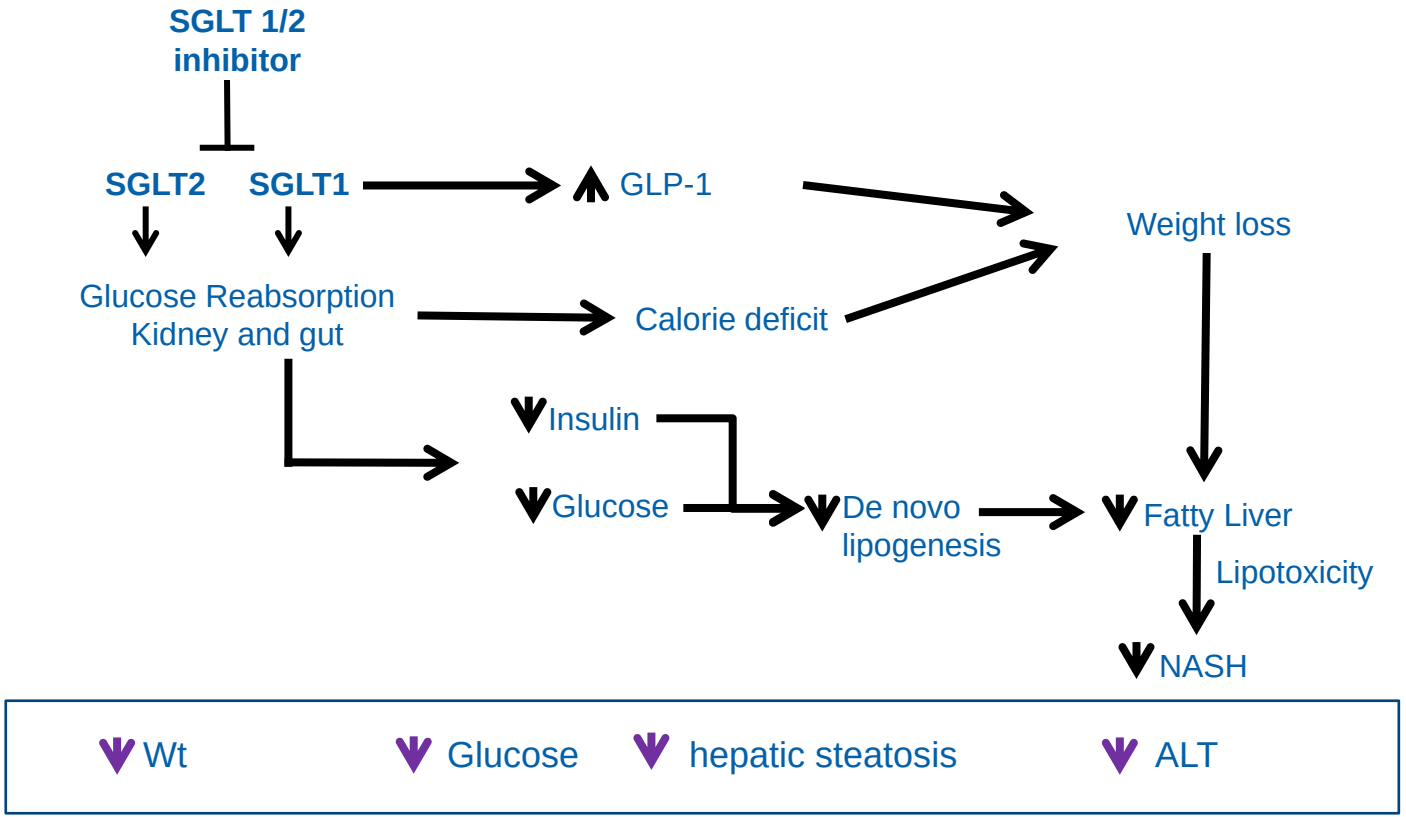
Hypothesis: LIK066 could improve multiple aspects of NASH



LIK066X2204 PoC Study Design

Study population

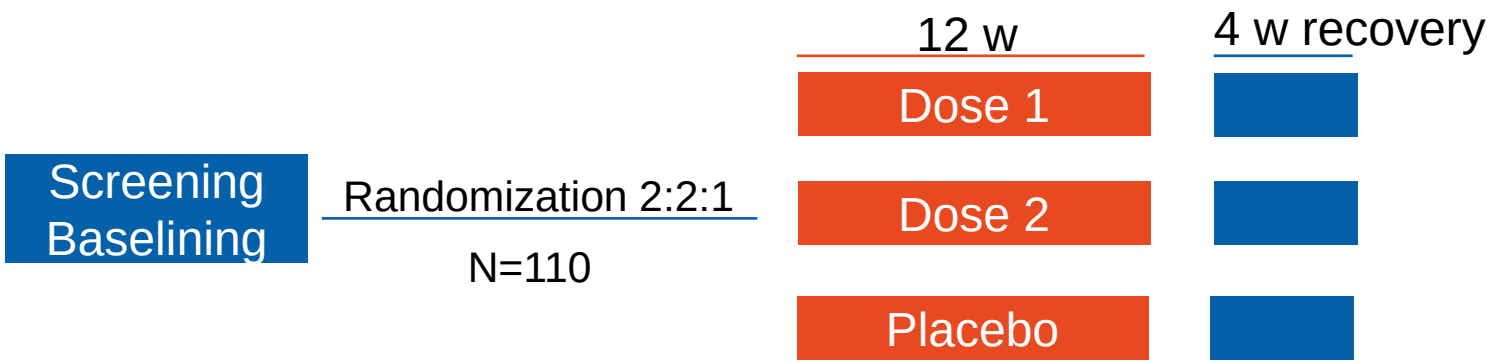
- Men, women age: >18 y with either of the following
- BMI: ≥ 27 (non-Asian) or ≥ 23 (Asian)
- ALT ≥50 (men), ≥ 35 (women)
- T2D with HbA1c ≥ 6.5

OR

- Prior liver bx c/w NASH with ALT ≥50 (men); ≥ 35 (women)

Key Endpoints

- 1º ALT
- 2º Safety/tolerability, liver fat by PDFF, body weight, ELF and components, AST



NCT03205150: Results expected 2019

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Summary

- Therapies that impact co-morbidities associated with NASH are likely to be beneficial in management of NASH patients
- LIK066, a potent SGLT1/2 inhibitor lowers blood glucose and insulin and increases post prandial incretin levels
- LIK066 leads to a marked decrease in body weight
- The beneficial metabolic effects may translate to significant impact on NASH
- A proof of concept study **(**NCT03205150) on patients with a phenotype suggestive of NASH is currently in progress

Thank you

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