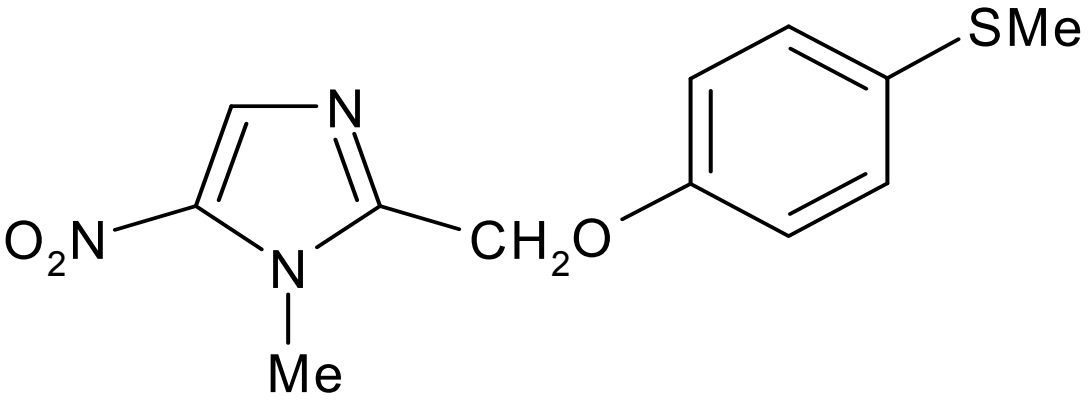
Fexinidazole a new oral treatment for sleeping sickness – update of development



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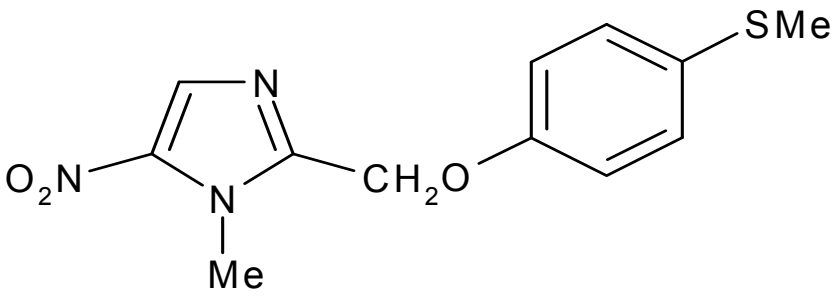
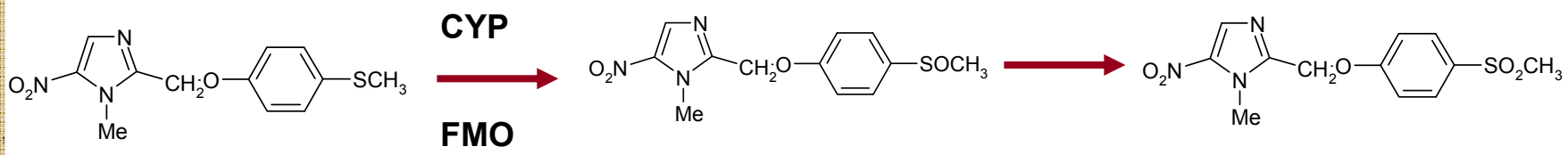
September 2011

Fexinidazole

- Discovery : 1970 HOE 239, discontinued 1980
- Chemical Name: 1H-imidazole,1-methyl-2-[[4-methylthio) phenoxy] methyl] 5-nitro-imidazole
- PM = 279.31 g/mol
- Metabolism





Fexinidazole **Fexinidazole sulfoxide (M1)** **Fexinidazole sulfone (M2)**

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In vitro activity of fexinidazole

IC_{50} values (µg/ml)

Compound Tested	***T.b. rhodesiense**** **(IC_{50})**	***T. b. brucei**** **(IC_{50})**	***T. b. brucei**** **(MIC)**
Fexinidazole (Batch 1)	1.265	2.86	5.00
Fexinidazole (Batch 2)	0.719	ND	ND
Fexinidazole sulfoxide	0.487	1.96	4.74
Fexinidazole sulfone	0.354	0.89	2.20

*Data from STI
**Data from SCYNEXIS

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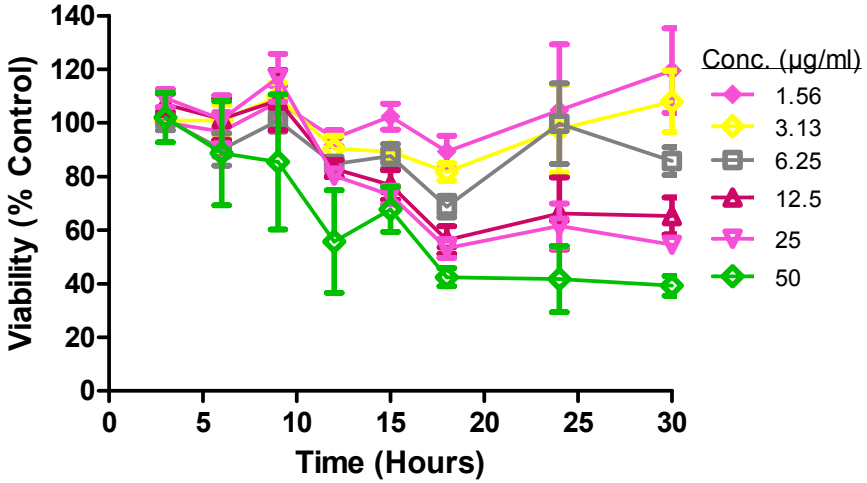
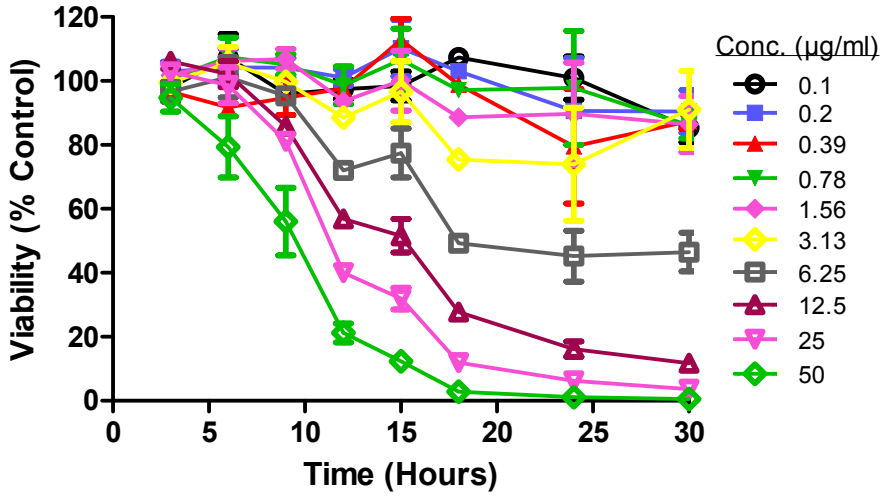
Time Kill Assays - Fexinidazole and Metabolites

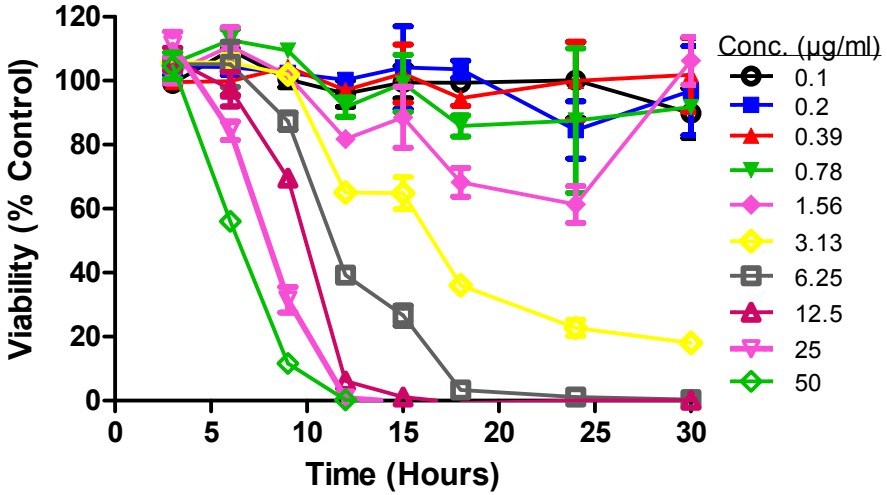
Fexinidazole (IC_{50} = 2.86 µg/ml)



Fexinidazole-Sulfoxide (IC_{50} = 1.96 µg/ml).



Fexinidazole sulfone (IC_{50} = 0.89 µg/ml)



Wash-out IC_{50} Values

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General pharmacology

- **Standard genotoxicity battery**
  - Ames — Ames -ve
  - In vivo micronucleus + test — negative
  - In vitro chromosomal aberration — negative
- **Enzymes, Radioligand Binding Assay**: 0< 10µM
- **hERG : partially + for M2**
- **Telemetry in Dog: negative**
  - NOEL CV parameters and ECG intervals ≥1000 mg/kg
- **Irwin test in rat**: general behavior and body temperature
  - NOEL ≥ 1000 mg/kg.
- **Respiratory Parameters in rat:**
  - NOEL ≥1000 mg/kg.

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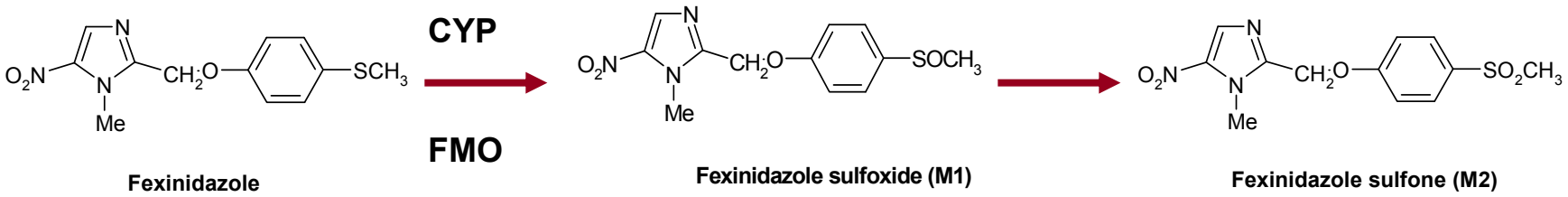
General pharmacology(2)

- Good intestinal permeability (Caco-2)
  no limiting factor for absorption
- Good potential for BBB permeability (MDR1-MDCK)
- High plasma protein binding
  Fexinidazole 95% (human); 93% (mouse)

- Metabolism



Fexinidazole **Fexinidazole sulfoxide (M1)** **Fexinidazole sulfone (M2)**

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Toxicology

NOAEL Rat + Dog: 200 mg/kg/Day

with a MTD at 800 mg/kg/d based on general toxicity, not hepatic effect

Reprotox : NOAEL 200mg/kg/day

RAT :NOAEL for the pregnant mother = 200 mg/kg/day

- NOAEL for the FO= 200 mg/kg/day
- NOAEL for the F1= 200 mg/kg/day

Phototox: Negative

Fexinidazole Clinical Studies

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Phase I studies

- So far 96 subjects have been dosed
- Part 1 (SAD) Study Design
  - oral suspension escalation from 100 up to 3600 mg
- Part 2 Cross-over bioequivalence and food effect Study
  - 1200 mg single dose
- Part 3 (MAD) Study Design
  - Three cohorts of 8 subjects (6 active, 2 placebo)
  - Oral tablet (600 mg) once a day for 14 days 1200mg,2400mg &3600mg
- Field food effect study (cross-over study)
  - Three cohorts of 12 subjects
- Multiple dose in fed conditon (on going)
  - Randomized , double- blind versus placebo
  - Two cohorts of 18 subjects (12active, 6 placebo)
  - Pop pk analysis

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PK Results

Bioavailability

- Fexi : rapidly absorbed: median Tmx: 3 – 4 H; mean T**1/2**: 9-15H
- M1 : occured rapid : median Tmx: 2-5 H; mean T**1/2**: 18-20H
- M2 : occurred slowly: median Tmx: 18-24 H; mean T**1/2**: 18-25H

Exposure **increased linearly**
but not proportional to dose administered

No saturation of the metabolism

Steady state : D4 for fexi and M1, D9 for M2

Free fraction in human : fexi 3 % M1 and M2 > 40%

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Safety results

SAD

- No serious nor severe Aes, no discontinuation
- No trends nor relevant changes vs baseline in VS, ECG, safety lab tests
- Few mild transient AES (headache)

MAD

- Some ΔQTcB increases in the 3600 mg - Holter results to com
- Headaches and Grastro intestinal disorders (mild or moderate) mostly transient – no pattern
- Liver enzymes increase
- 2 SAEs

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Frequency of ALT/AST increases

ALAT	cohort 1	cohort 2	cohort 3
dose	1200 mg	2400 mg	3600 mg/
nb volunteers	8	9*	8**
≤1N	3	8	6
1N<x≤2N	4	1	
2N<x≤3N	1		1
3N<x≤30N			
30N<x≤40N			1

ASAT	cohort 1	cohort 2	cohort 3
dose	1200 mg	2400 mg	3600 mg
nb volunteers	8	9*	8**
≤1N	6	5	6
1N<x≤2N	1	2	1
2N<x≤5N			
5N<x≤6N		1	
6N<x≤9N			
9N<x≤10N	1		
10N<x≤30N			
30N<x≤40N			1

*one subject dropped on D9 with follow up until D28

** one subject stopped on D6 with follow up until D28

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ECG QT/QTC Results

Categorical analysis for triplicate holter QTc

		Fexinidazole		
	Placebo (N=6)	1200 mg (N=6)	2400 mg (N=6)	3600 mg (N=6)
	n (%)	n (%)	n (%)	n (%)
Changes in QTcF (ms)				
ΔQTc>30 ms	0 (0.0)	2 (33.3)	2 (33.3)	2 (33.3)
ΔQTc>60 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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PK Food effect

Food effect 1200mg (2X600mg) single dose

- relative bioavailability Cmax and AUC_{0-t}:
  - 4 fold increase in the extend of absorption of fexinidazole
- - M1 & M2 increased proportionally
- - intra-individal variability:
  - Cmax and AUC_{0-t} markedly reduced (10 – 15%)

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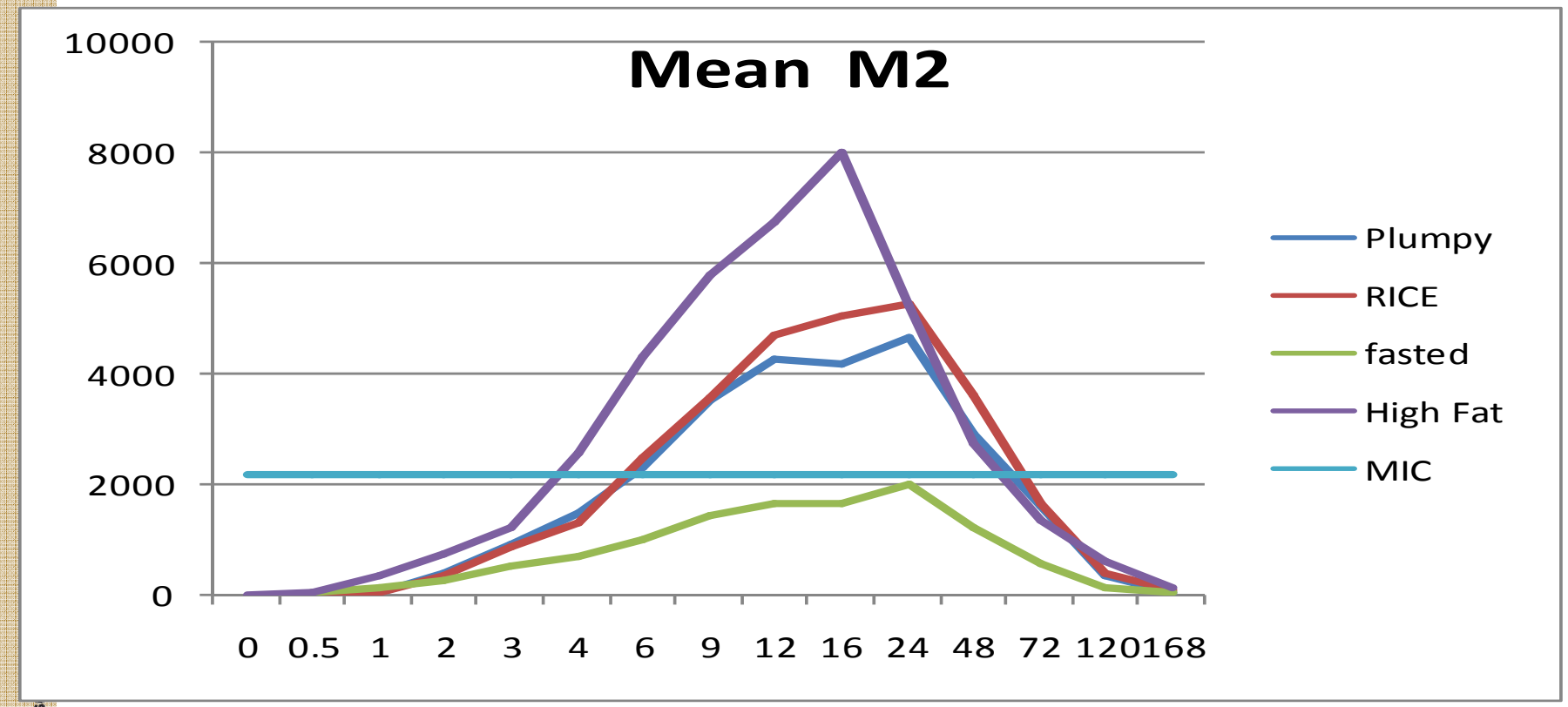
M2 Mean Plasma levels



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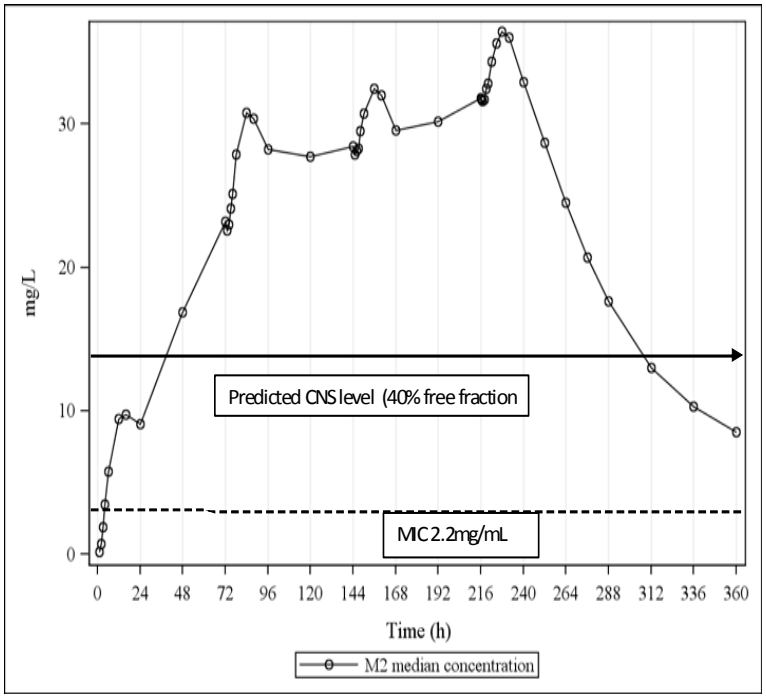
POP PK calculations

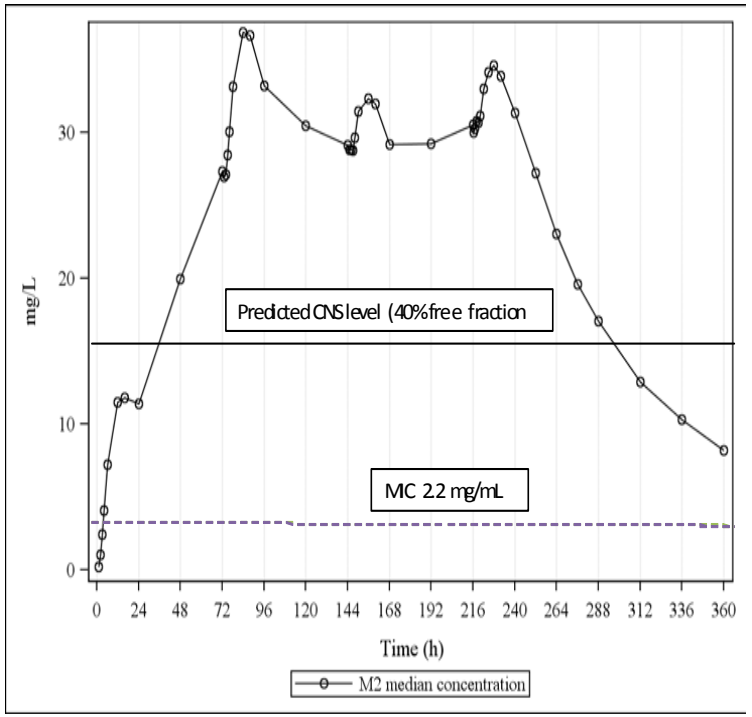
Dose regime 1= 1800mg(QD) for 4 days +1200 mg (QD) for 6 days

Dose regime 2= 2400mg(QD) for 4 days +1200 mg (QD) for 6 days

Dose regimen 1800 mg (D1-D4)+1200 mg(D6-D10)



Dose regimen 2400 mg (D1-D4)+1200 mg(D6-D10)



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Fexinidazole
Next Steps

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NEXT studies

- Validation of the highest safety and efficacy dose
- Phase II/III study 2012
- Study in stage 1 of HAT with the same dose

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Vision for FEXINIDAZOLE

- **H**aving oral efficacy and safety dose
- **A**vailable as once a day dosing
- **T**reatment for all stages of the disease

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Thank you

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