Realizing the Next Revolutions in TB Treatment
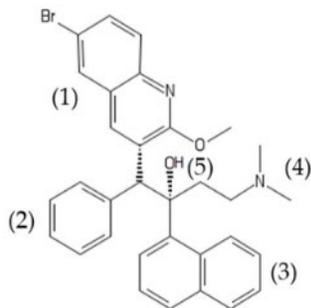
A case study of TB drug and regimen development

Pretomanid: novel compound
- Active against replicating and non-replicating TB

Bedaquiline

Linezolid

BPaL regimen
- 3 novel drugs without pre-existing resistance
- Individual contributions shown in mouse model

TB Practecal
- Superiority of BPaL/M vs. SOC
- Broadened to RR-TB

ZeNix Trial
- Linezolid 1200 → 600 mg
- Maintained 90% efficacy
- Reduced linezolid toxicity

Nix-TB Trial
- 90% cure in highly resistant TB with 6-month treatment
- FDA and EMA approval of BPaL

WHO Guidelines for drug-resistant TB
Treatment of choice for most DR-TB

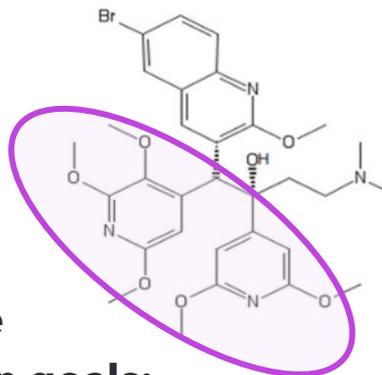# What is sorfequiline and why it is important

BDQ

Bedaquiline (BDQ)
- First-in-class diarylquinoline (DARQ)
- Novel mechanism of action
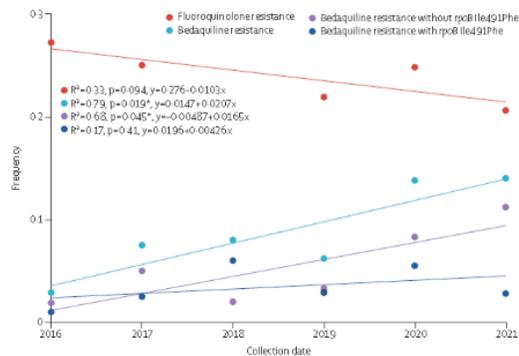- QT prolongation
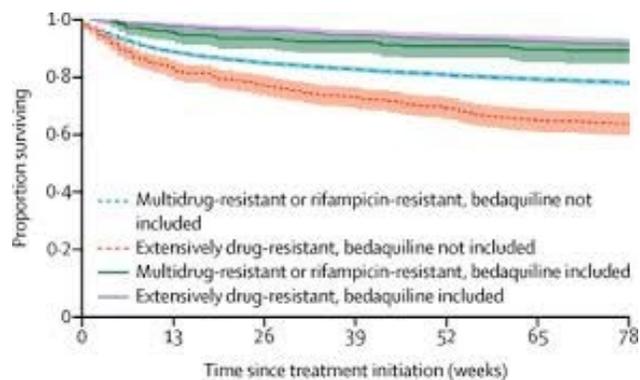
SFQ

Sorfequiline (SFQ) design goals:
- Increase potency
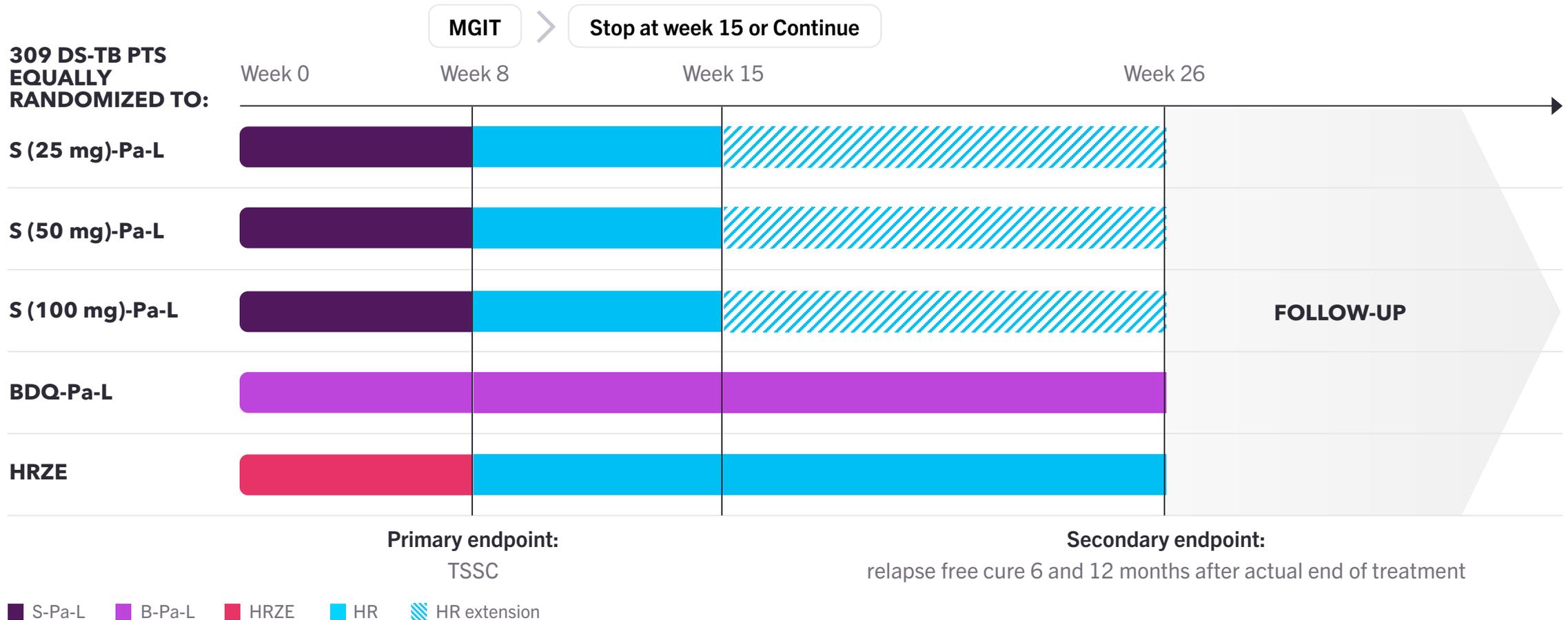- Reduce/eliminate QT effect

10x greater potency compared with BDQ

- ✓ Potential to shorter treatment duration
- ✓ Lower likelihood of resistance emerging
- ✓ Activity against BDQ-resistant strains

No QT prolongation observed in preclinical or clinical studies

NC-009 efficacy at week 8 - MITT

KM PROBABILITY OF SCC BY WEEK 8*

HR 1.34# (0.81, 2.23)

HR 1.49# (0.91, 2.46)

S 25 N=58	S 50 N=64	S 100 N=60	BPaL N=63	HRZE N=59
31%	48%	59%	45%	45%
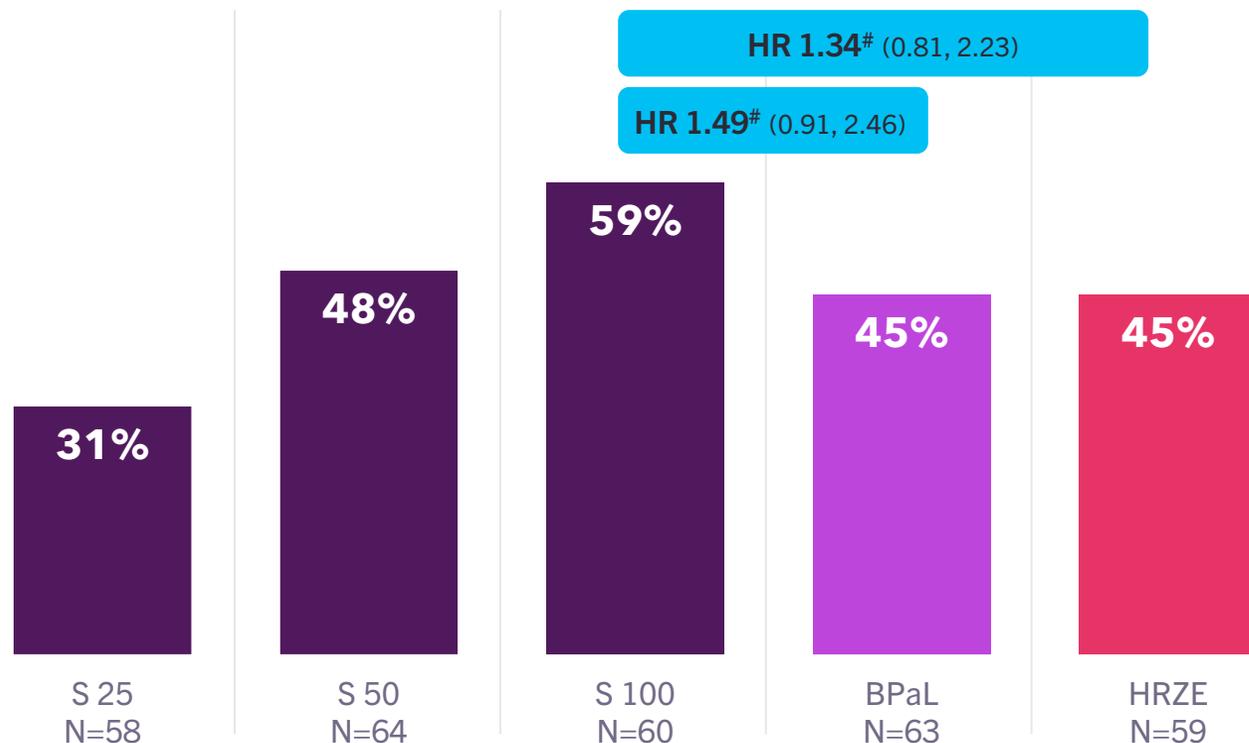
✓ Clear dose-response in sorfequiline arms

✓ 100 mg sorfequiline arm outperforms BPaL and HRZE

* Kaplan Meier method
** Stratified Cox Proportional Hazard model

NC-009 safety summary through 8 weeks
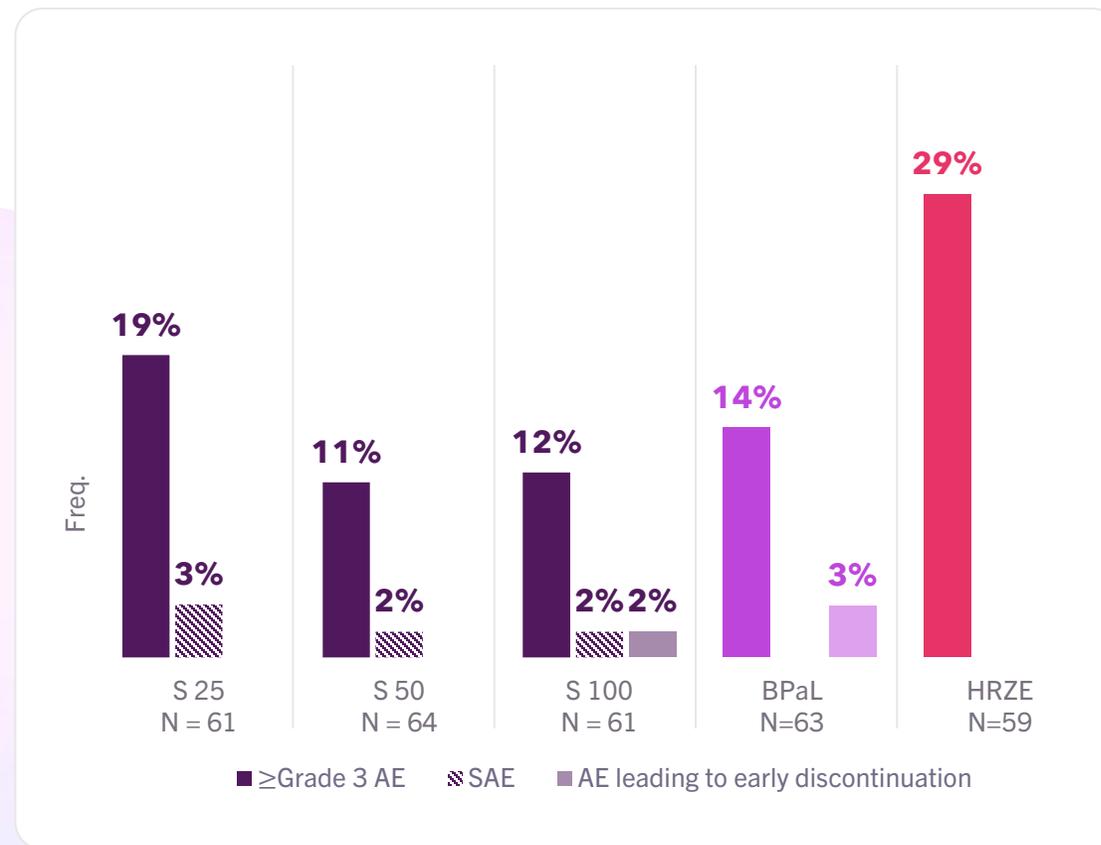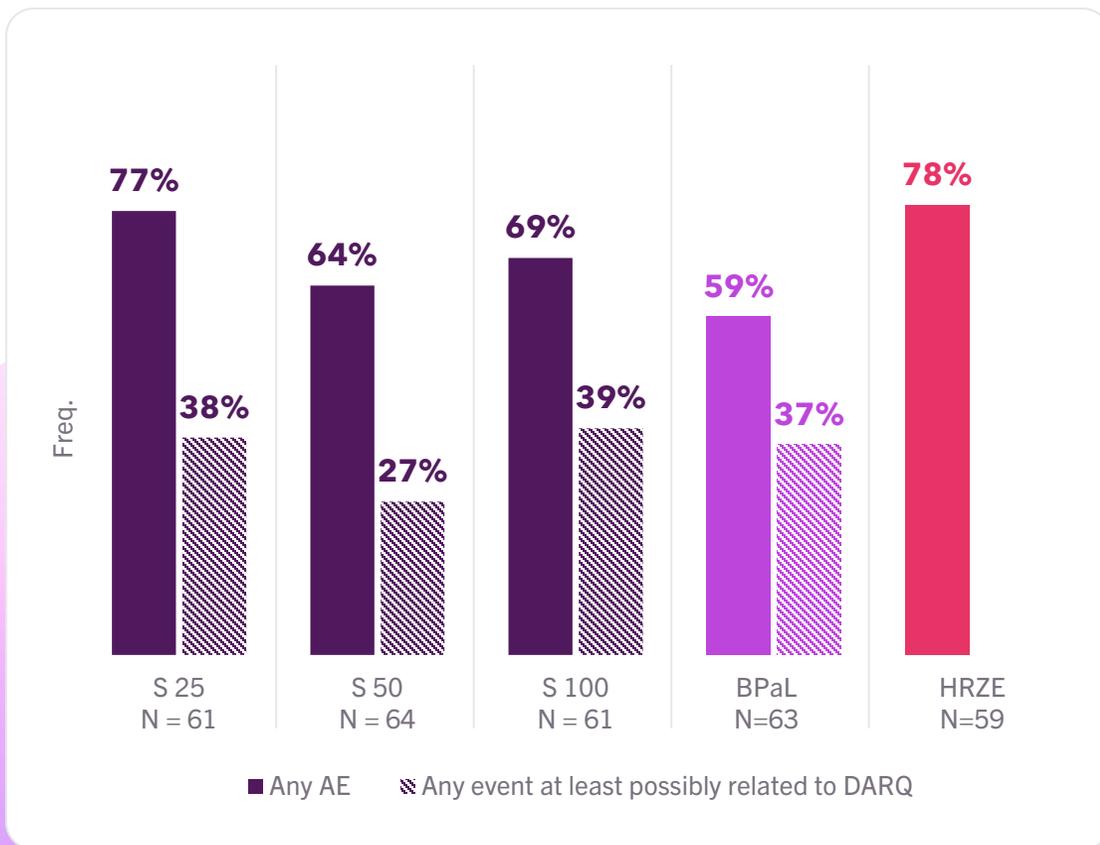

NO DOSE EFFECT OF SORFEQUILINE ON FREQUENCY OF AES REGARDLESS OF SEVERITY

Microbiological relapse rate 26 weeks after end of treatment

Treatment week

| Week 0 | Week 8 | Week 15 | Week 26 |

S (100 mg)-Pa-L — 1/36*

1/24

BDQ-Pa-L — 1/63

HRZE — 1/59

RELAPSE RATE: S (25 mg)-Pa-L (15-week= 4/15; 26-week= 8/43). **S (50 mg)-Pa-L** (15-week= 0/28; 26-week= 4/36).
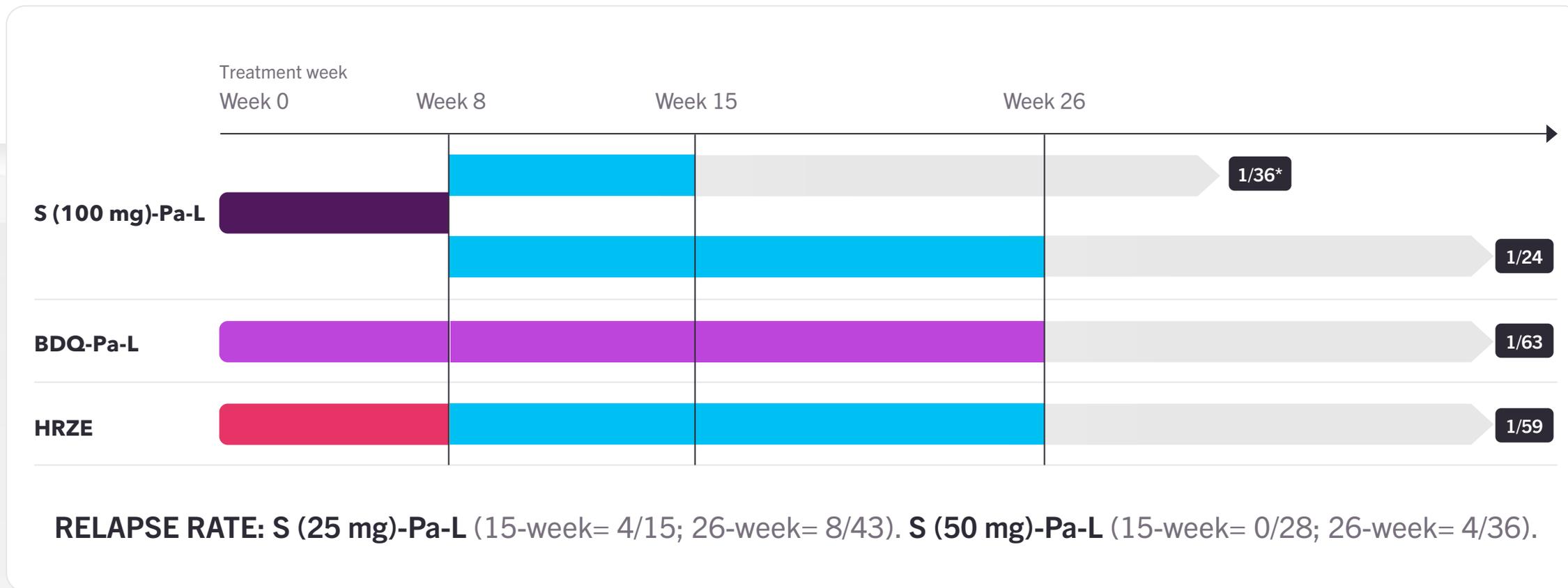
■ S-Pa-L   ■ B-Pa-L   ■ HRZE   ■ HR   ■ Follow-up 6-12 month

*early Stable Culture Conversion (week 5), asymptomatic at recurrence, possible reinfection from infected but untreated roommate

NC-009 demonstrates

✓ 100 mg SPaL regimen has greater bactericidal activity than BPaL or HRZE

✓ Data supports a 4-month regimen

✓ Unremarkable safety profile

✓ Favorable QTc profile versus bedaquiline

SORFEQUILINE: A PHASE 3-READY DRUG CANDIDATE

Sorfequiline Phase 3 study

Randomize ~500 Stratified by:
- Disease severity
- FQ susceptibility

SPaL/M x 4 months | 1-year **FOLLOW-UP**

BPaL/M x 6 months | 1-year **FOLLOW-UP**

Primary endpoint:
Outcome at 12 months after treatment initiation

Randomized, controlled, multinational non-inferiority trial in **DRUG-RESISTANT TB (DR-TB)**

✓ 4-month regimen of SPaL/M (moxifloxacin)

✓ 6-month regimen of BPaL/M (WHO standard of care for DR-TB)

Drug-resistant TB classification

Rif-resistant	Multidrug-resistant	Pre-Extensively drug-resistant	XDR (extensively drug-resistant)
Rifampicin	RIF **and** INH	RIF + INH + FQ	RIF + INH + FQ + **BDQ** or **Lzd**
Included in sorfequiline Phase 3 study			**Exploratory**

Roadmap to next transformational treatment paradigms

Sorfequiline/SPaL

NC-009

↓

Phase 3 study

↓

Registration

ONE MONTH
Oral/LAI Regimen development

ORAL REGIMEN OF

SPaL(X)

Given for 30 days

No pre-existing resistance

1 month

SINGLE INJECTION OF

SPa(X)

Therapeutic for 3+ months

Long-acting injectables (LAI) technology

LAI Development:
- Sorfequiline
- Telacebec
- Pretomanid
- Others
- TBAJ-587

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Sorfequiline or TBAJ-587 1-shot treatment for Latent TB

X = additional TB drug with oral/LAI formulations, e.g., TBD11 from GMRI