PARADIGM-HF: Are There Any Controversies?

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Presenter Disclosure Information

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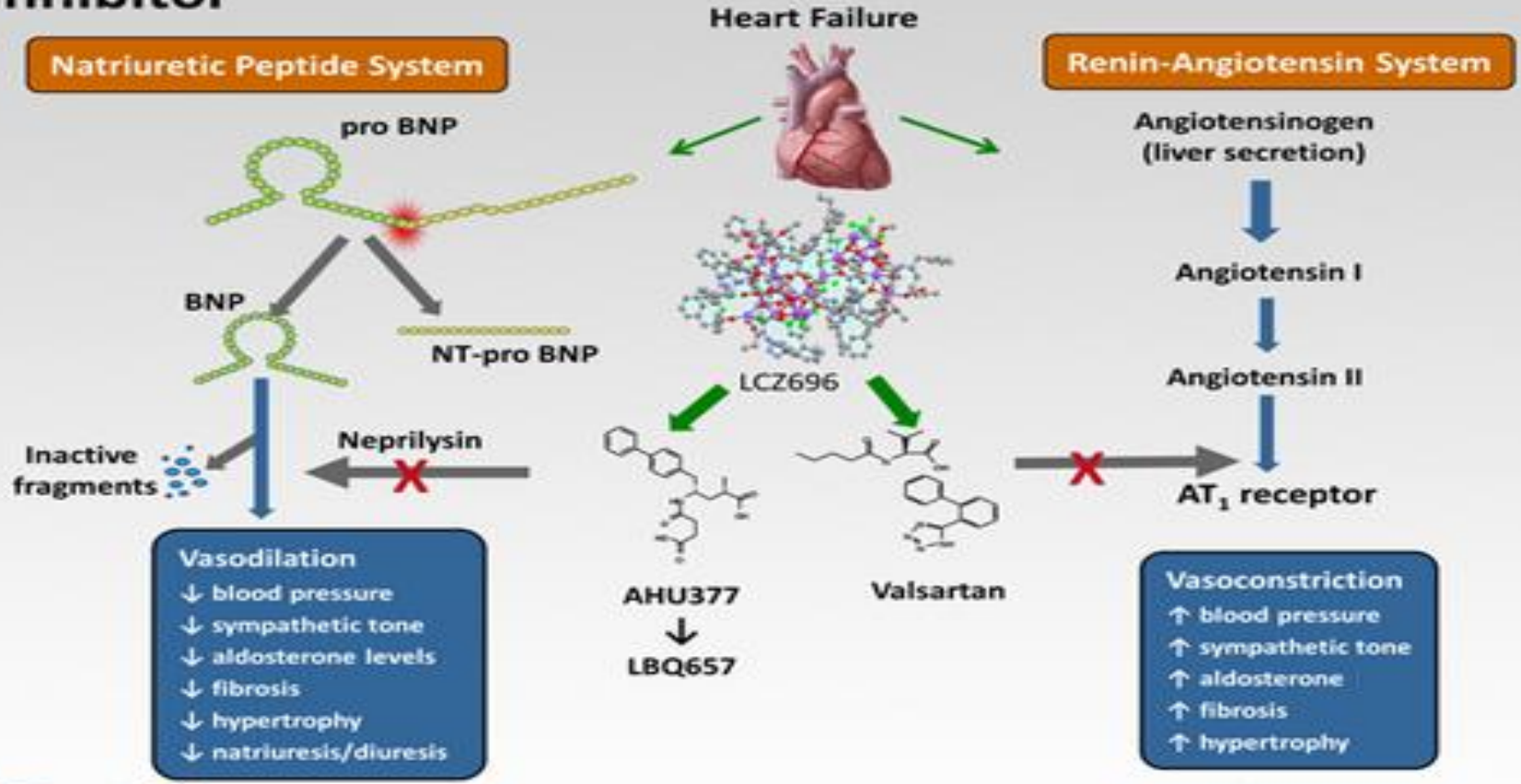
- I am on the speaker's bureau for BMS, Pfizer, Daichi-Sankyo, Novartis
- I will not discuss off-label or investigational use in my presentation.

LCZ696: A First-in-Class Angiotensin Receptor Neprilysin Inhibitor



PARADIGMHF

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Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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Aim of the PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

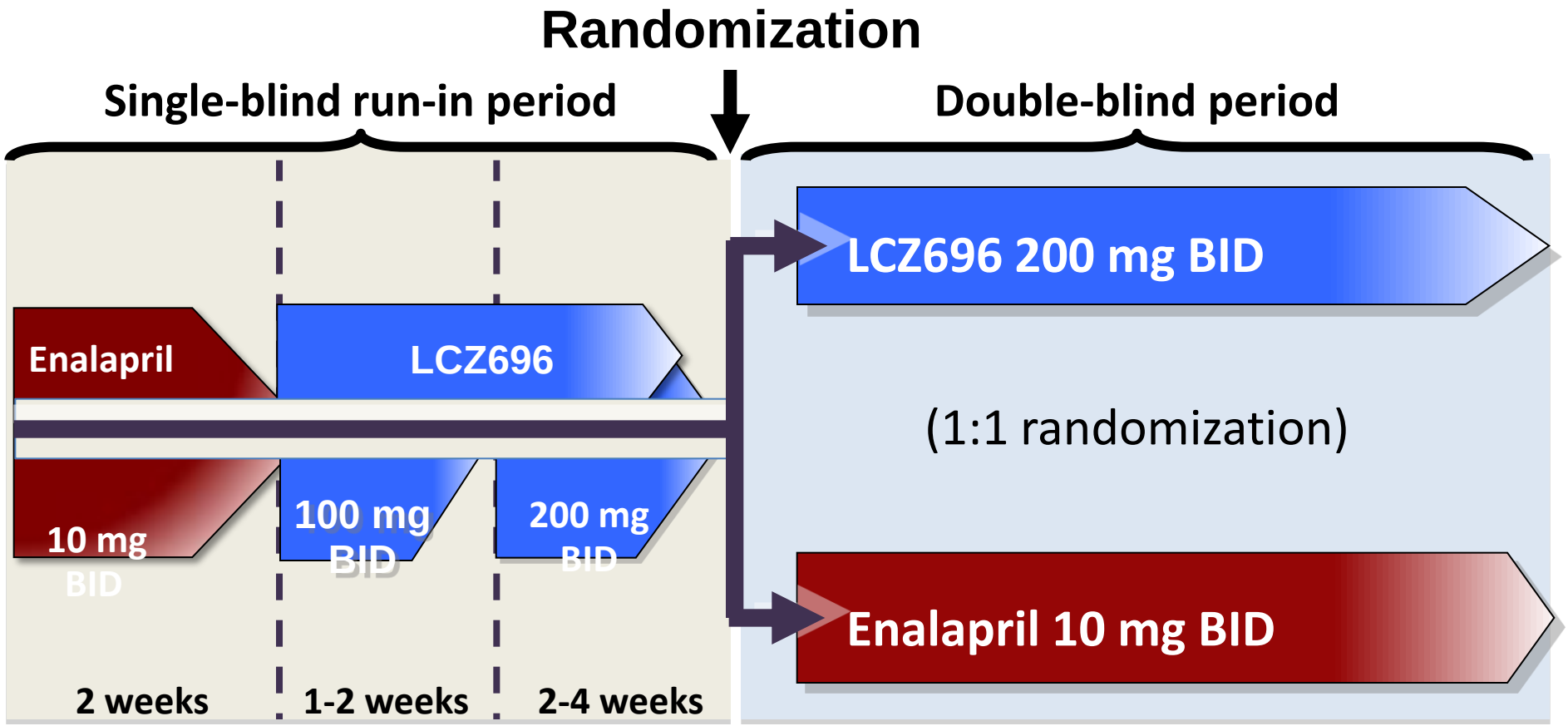
LCZ696 400 mg daily ⟷ **Enalapril 20 mg daily**

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

PARADIGM-HF: Entry Criteria

- NYHA class II-IV heart failure, LV ejection fraction ≤ 40% ➔ 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m^2 and serum K ≤ 5.4 mEq/L at randomization

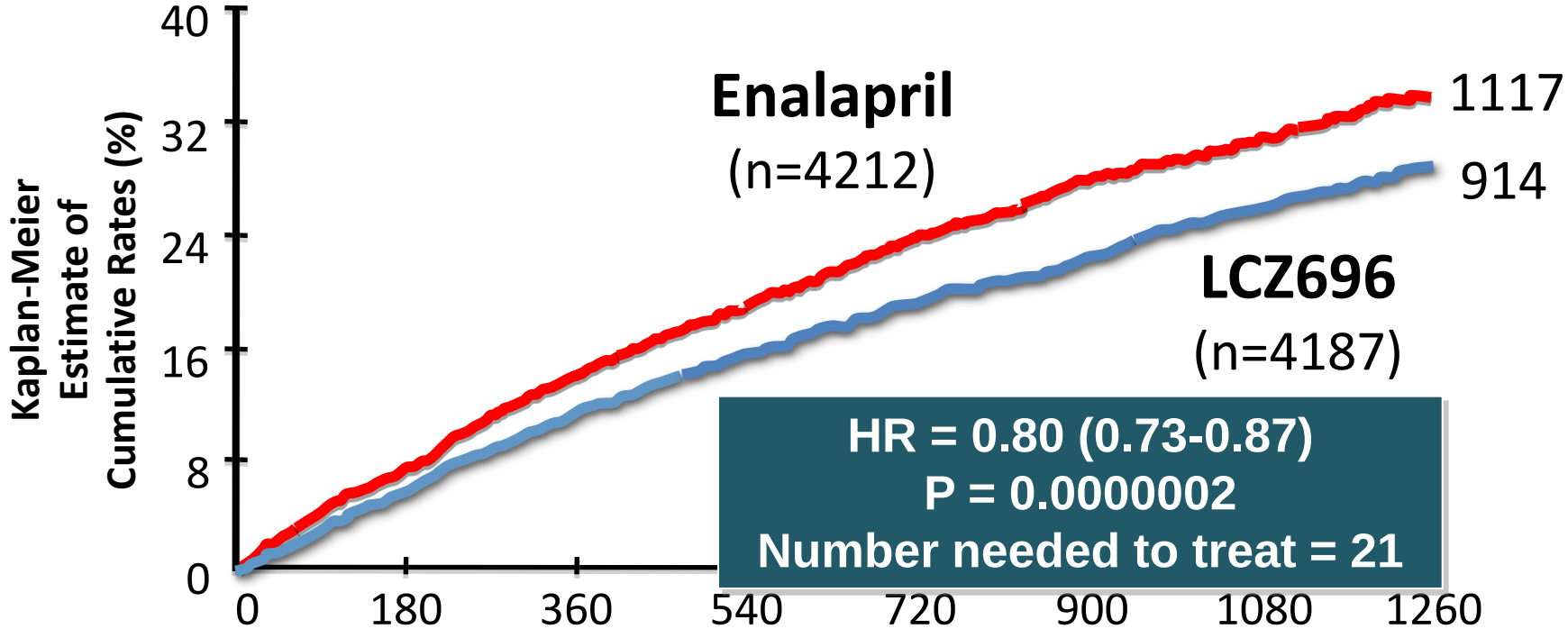
PARADIGM-HF: Study Design



PARADIGM-HF: Baseline Characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

LCZ696 was *more effective* than enalapril in . . .

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

LCZ696 was *better tolerated* than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure 2016

(Yancy et al.,**Circulation**, September 6, 2016, Vol.134, Issue 10)

- **Class I indication:** Inhibition of RAS with ace-inhibitors, OR ARBs, OR ARNI in conjunction with evidence based beta-blockers, and aldosterone antagonists in selected patients is recommended for patients with chronic HFrEF to reduce morbidity and mortality
- **Class I indication:** In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE-inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality

“Straw Man” Comparator

- Were the results seen in PARADIGM-HF merely due to the fact that there was less RAS inhibition with medium dose enalapril (20mg vs 40mg daily) vs maximum dose valsartan (320mg daily)?
  - CONSENUS (1987), 18mg/day
  - SOLVD-treatment (1991), 17mg/day
  - V-HeFT II (1991), 15mg/day
  - PARADIGM-HF (2014), 18.9mg/day (highest dose of enalapril ever used in a clinical trial)

Run-In Phase of PARADIGM

- PARADIGM had an active run-in phase in which 19.8% of patients dropped out (10.5% in enalapril, 9.3% in entresto). 2/3 of these discontinuations were due to hypotension, hyperkalemia, worsening renal function.
- There are no active run-in phases in the real world setting.
- Run-in phase improves internal validity of results as fewer discontinuations to be expected, but reduce external validity
- In the randomized population, more patients in the ARNI group experienced symptomatic hypotension (18% vs 12%). Would expect to see considerably more hypotension in the real world setting
- TITRATION study demonstrated in 498 patients that (76%) patients achieved and maintained sacubitril/valsartan 200 mg twice daily without dose interruption/down-titration over 12 weeks. Also more gradual initiation/uptitration (6 wk vs 3 wk) maximized attainment of target dose in the low-dose ACEI/ARB group (Senni et al. Eur J Heart Fail. 2016 Sep;18(9):1193-202)

Entresto Dosing

Generalizability

- **Patient characteristics:** PARADIGM enrolled a select group of young patients. The mean age was 63 years; 80% were male, and only 6% were black (How do these data apply to elderly non-Caucasian women?)
- **Lack of NYHA class IV patients**: PARADIGM-HF was a trial with predominately stable (NYHA class II) patients (<1% NYHA class IV patients).
  - despite the label NYHA class II-IV, HF guidelines do not mention NYHA class IV patients, most HF experts have not advocated use of entresto in this population as of yet
- **BP inclusion criteria**: (Mean BP of 120mmHg at baseline on bb and ace-i), when was the last time a low EF patient had that good a blood pressure?

Alzheimer’s Dementia

- Neprilysin is one of multiple enzymes able to degrade amyloid-β (Aβ); its inhibition may increase Aβ levels.
- Aggregable Aβ isoforms are known to accumulate in Alzheimer's disease.
- A theoretical and unproven potential exists that treatment with LCZ696 (angiotensin receptor neprilysin inhibitor) may result in the accumulation of Aβ isoforms.

Alzheimer's Dementia

- Animal studies:
  - Aged, neprilysin knock-out mouse; associated with increased Aβ accumulation in the brain and leads to deposition of amyloid-like structures in vivo as well as with signs of AD-like pathology and with behavioral deficits (Madani et al J Neuroscience Research, Volume 84, Issue 8 December 2006 Pages 1871–1878)
  - Young (2 to 4 years old) cynomolgus monkeys treated with ENTRESTO (24 mg sacubitril/26 mg valsartan/kg/day) for 2 weeks demonstrated increasing CSF Aβ 1-40, 1-42, and 1-38 levels in CSF; there was no corresponding increase in Aβ levels in the brain. In addition, in a toxicology study in cynomolgus monkeys treated with ENTRESTO at 146 mg sacubitril/154 mg valsartan/kg/day for 39-weeks, there was no amyloid-β accumulation in the brain (Entresto Package Insert)

- Human volunteers: Once daily LCZ696 (400 mg) for 14 days does not cause changes in CSF levels of aggregable Aβ isoforms 1–42 and 1–40 compared with placebo, despite achieving CSF concentrations sufficient to inhibit neprilysin. The clinical relevance of the increase in CSF Aβ 1–38 is unknown (Langenickel TH Br J Clin Pharmacol. 2016 May; 81(5): 878–890.)

- Conclusion: No cognition issues were seen in PARADIGM, but the 2.5-year trial was not designed to assess a problem that may accrue over the long term (long-term extensions studies and PARAGON plan to evaluate this further)

$4500 per year, $12.50/day

From: **Cost-effectiveness Analysis of Sacubitril/Valsartan vs Enalapril in Patients With Heart Failure and Reduced Ejection Fraction**
JAMA Cardiol. Published online June 22, 2016. doi:10.1001/jamacardio.2016.1747

Table 2. Total Costs, Health Effects, and Incremental Cost-effectiveness Ratio

	Costs, $		QALYs		
	Total	Incremental	Total	Incremental	ICER, $
Enalapril	83 303		6.02		
Sacubitril/valsartan	118 815	35 512	6.80	0.78	45 017

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYS, quality-adjusted life-years.

Table Title:
Total Costs, Health Effects, and Incremental Cost-effectiveness Ratio

Sacubitril/valsartan was cost-effective

- Standard-accepted levels for evaluations of new therapies and interventions (ACC/AHA and World Health Organization)
  - “very good value” (<$50 000 per QALY)
  - “good value” (<$150 000 per QALY)
- ICER for pravastatin before it became generic was $54 000 to $1.4 million per QALY gained
- ICERs for implantable cardioverter defibrillators with and without cardiac resynchronization therapy range from $35 000 to $108 000 per QALY
- ICERs for percutaneous coronary interventions are approximately $36 000 per QALY
- ICER for left ventricular assist devices range from $120 000 to more than $300 000 per QALY gained

Unanswered Questions

- Use in the setting of acute heart failure (ASCEND-HF trial with niseritide) (PIONEER safety change in nt-bnp endpoint)
- Approximate 50% of heart failure patients with HFpEF (PARAGON study)
- Tolerability in large population outside of clinical trial setting
- How to handle symptomatic hypotension
  - cut back on diuretics, stop non-essential bp lower meds such as alpha blockers and nitrates, consider reducing dose of coreg or switching from coreg to toprol xl, holding MRAs during up-titration of entresto
- Effect of Entresto on improvements in myocardial structure and function
- Novartis has announced Fortifying Heart Failure clinical evidence and patient quality of life (FortiHFy): an umbrella clinical program comprising over 40 active or planned trials