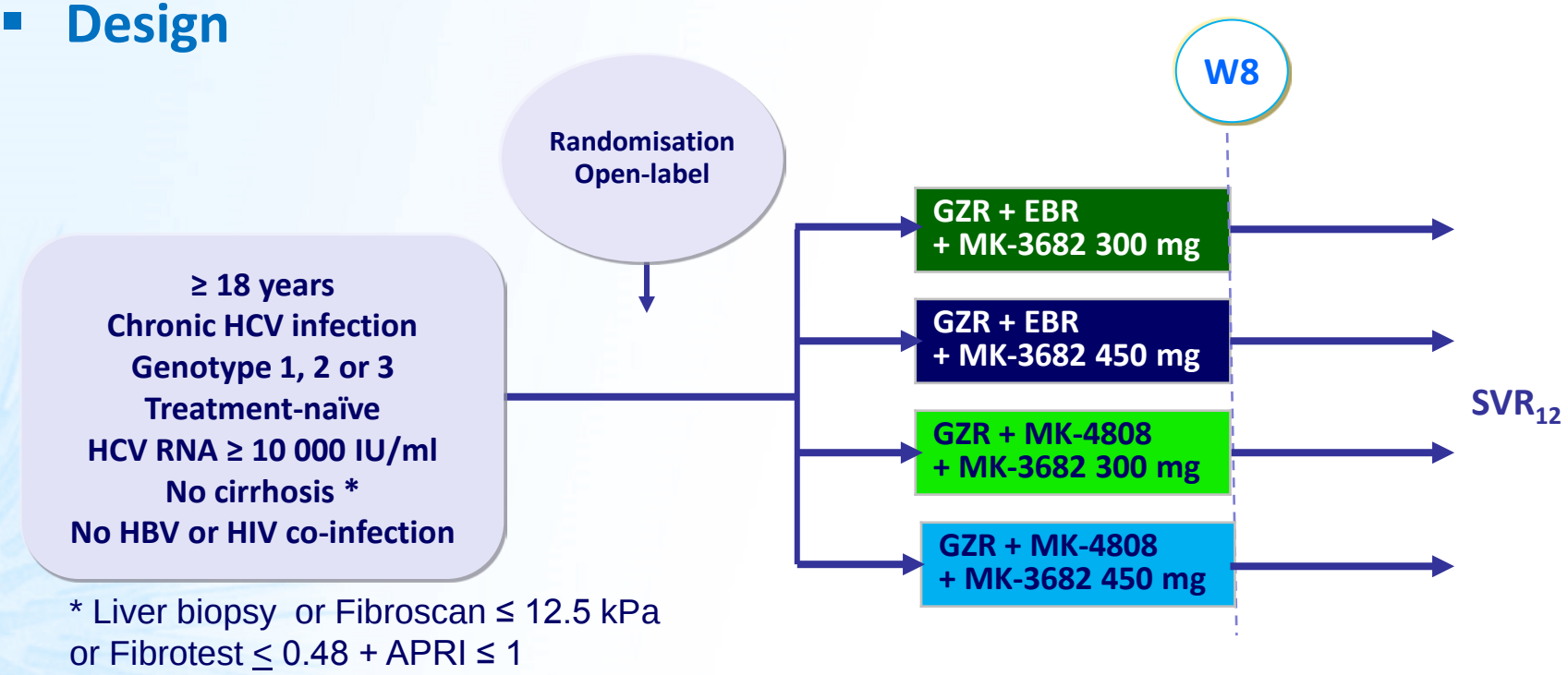
C-CREST study, Part A: GZR + EBR or MK-8408 + MK-3682 for genotypes 1, 2 and 3 - Phase II

- **Design**



* Liver biopsy or Fibroscan ≤ 12.5 kPa
or Fibrotest ≤ 0.48 + APRI ≤ 1

  - GZR: 100 mg qd ; EBR: 50 mg qd ; MK-4808: 60 mg qd

- **Objective**
  - Primary endpoint: SVR_{12} (HCV RNA < 15 IU/mL)

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Baseline characteristics

	GZR + EBR + MK-3682 300 mg N = 60	GZR + EBR + MK-3682 450 mg N = 60	GZR + MK-4808 + MK-3682 300 mg N = 59	GZR + MK-4808 + MK-3682 450 mg N = 61
Median age, years	48	49	49	47
Female	43%	62%	56%	46%
Race, white	90%	92%	97%	95%
HCV genotype, n				
1a	11	10	16	9
1b	12	13	8	14
2	16	15	14	16
3	21	22	21	22
Metavir				
F0-F2	85%	98%	93%	93%
F3	15%	2%	5%	7%
HCV RNA $\log_{10}$ IU/ml, median	6.3	6.0	6.1	6.2

- All 240 enrolled patients completed 8 weeks of treatment and reached follow-up W12 post-treatment

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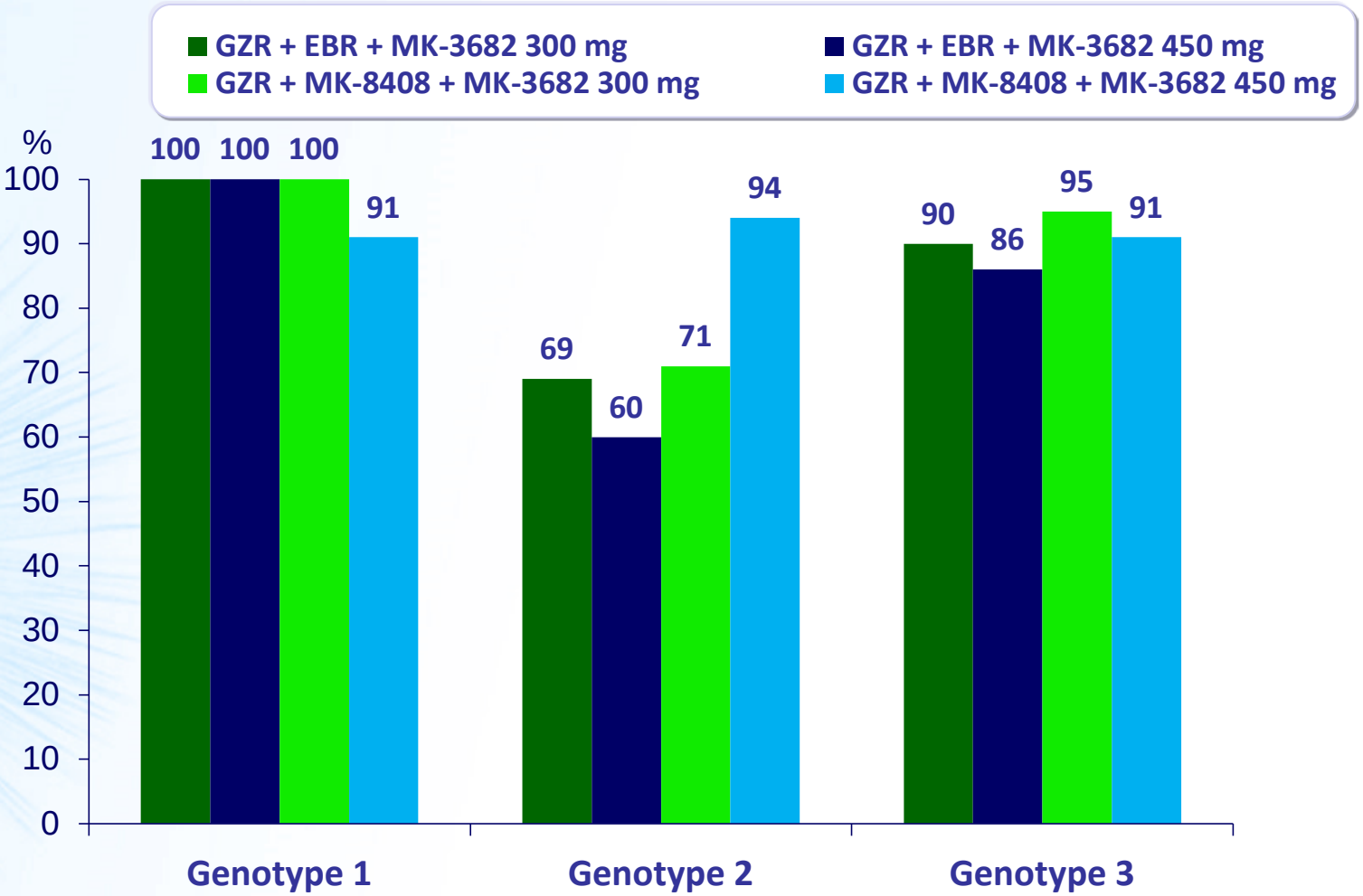
SVR_{12} (HCV RNA < 15 IU/mL), full analysis set



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C-CREST study, Part A: GZR + EBR or MK-8408 + MK-3682 for genotypes 1, 2 and 3 - Phase II

- **Impact of baseline NS5A RAVs**
  - No impact of baseline genotype 1 NS5A RAVs on SVR_{12}
    - SVR_{12}: 97% if no RAVs, 100% if RAVs
    - No treatment emergent NS5A RAVs in the 2 relapses (1 genotype 1a and 1 genotype 1b)
  - High SVR_{12} in genotype 3 with GZR + MK-4808 + MK-3862 despite high prevalence (47%) of NS5A RAVs
    - SVR_{12}: 100% if no RAVs, 85% if RAVs
    - Treatment-emergent NS5A RAV in 1 of the 3 relapses (Y93H)

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C-CREST study, Part A: GZR + EBR or MK-8408 + MK-3682 for genotypes 1, 2 and 3 - Phase II

Impact of baseline RAVs (15% sensitivity threshold) on SVR_{12}

		Absent, N (%)	SVR_{12}		Present, N (%)	SVR_{12}
Genotype 1 N = 92	NS5A RAVs	70 (76%)	97%		22 (24%)	100%
	NS3 RAVs	38 (41%)	97%		54 (59%)	98%
	NS5B RAVS	73 (79%)	99%		19 (21%)	95%
Genotype 2 N = 16	NS5A RAVs	1 (6%)	100%		15 (94%) ; L31M = 8/15	93%
	NS3 RAVs	1 (6%)	100%		15 (94%)	93%
	NS5B RAVS	15 (94%)	93%		1 (6%)	100%
Genotype 3 N = 42	NS5A RAVs	22 (52%)	100%		20 (48%)	85%
	NS3 RAVs	4 (10%)	100%		38 (90%)	92%
	NS5B RAVs	41 (98%)	93%		1 (2%)	100%

- In genotype 1: no impact of baseline RAVs on SVR_{12}
- In genotype 2: high efficacy despite high prevalence of baseline NS5A and NS3 RAVs
- In genotype 3: modest impact of baseline NS5A RAVs on SVR_{12}

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Analysis of 6 failures on MK-3682 (300 or 450 mg) + GZR + MK-4808

	Dose of MK-3682	Genotype	Failure W		Baseline RAVs	RAVs at failure
1	450 mg	1a	FW24	NS3	WT	WT
				NS5A	WT	WT
				NS5B	WT	WT
2	450 mg	1b	FW12	NS3	Y56F, V170I	56F, V170I
				NS5A	WT	WT
				NS5B	C316N	C316N
3	450 mg	2b	FW12	NS3	K122R, I132L	K122R, I132L
				NS5A	T24S, F28L, L31M	T24S, F28L, L31M
				NS5B	WT	WT
4	300 mg	3a	FW24	NS3	V170I	V170I
				NS5A	A30K, S62T	A30K, S62T, Y93H
				NS5B	WT	WT
5	450 mg	3a	FW24	NS3	V170I	V170I
				NS5A	S62L/I, Y93H	S62L/I, Y93H
				NS5B	WT	WT
6	450 mg	3b	FW12	NS3	V170I	V170I
				NS5A	A30K, L31M, S62D	A30K, L31M, S62D
				NS5B	WT	WT

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Adverse events

	GZR + EBR + MK-3682 300 mg N = 60	GZR + EBR + MK-3682 450 mg N = 60	GZR + MK-4808 + MK-3682 300 mg N = 59	GZR + MK-4808 + MK-3682 450 mg N = 61
Drug-related adverse event	42%	48%	49%	46%
Serious adverse event, n	1	1	0	0
Drug-related serious adverse event, n	0	0	0	0
Discontinuation due to adverse event	0	0	0	0
Adverse event in > 10% of patients				
Headache	15%	27%	24%	26%
Fatigue	15%	25%	17%	21%
Nausea	8%	20%	12%	13%
Laboratory abnormalities				
Haemoglobin < 10 g/dl	0	0	0	0
Bilirubin > 5 x baseline	0	0	0	0
Late AST/ALT > 5 x ULN	0	0	0	1
Creatinine elevation, grade 1	0	0	0	0

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C-CREST study, Part A: GZR + EBR or MK-8408 + MK-3682 for genotypes 1, 2 and 3 - Phase II

Summary

- In this pilot phase II, randomised, open-label study, treatment with GZR + MK-4808 + MK36-82 was well tolerated and resulted in high rates of SVR_{12} (91–94%) in treatment-naïve non-cirrhotic patients with genotypes 1, 2 or 3
  - Improved SVR_{12} (85%) in patients with genotype 3 and baseline NS5A RAVs
- Good safety and tolerability
- GZR/MK-4808/MK3682 (450 mg) selected for study Part B

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