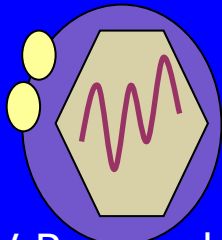


Real World Data usage in HCV (The story of NHSE compassionate program)

**Dr. Dimitar Tonev
on behalf of HCV research UK**

Cambridge, Novemeber 3rd 2017



HCV Research UK

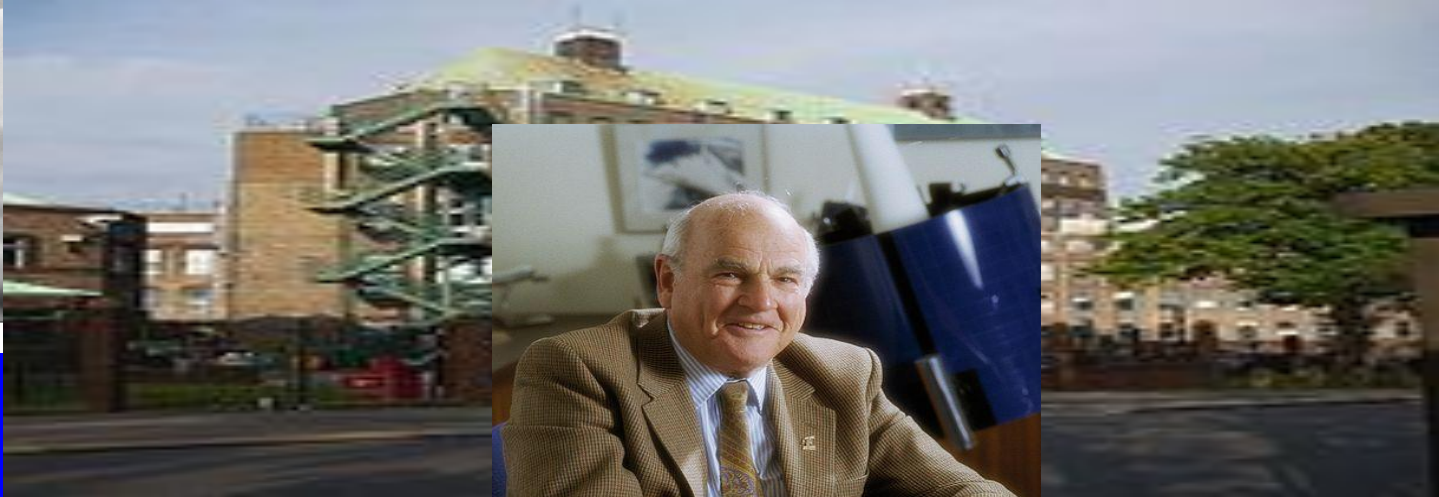


Slides prepared and kindly provided by Will Irving, John McLauchlan and Michelle Cheung

Disclosures

- The author is a pharmaceutical physician employed by Promethera Bioscience and has also been a BMS employee at the time of events described
- The author is a honorary consultant of HCV Research UK
- Opinions expressed are these of the author and not necessarily Promethera, BMS or HCV Research UK
- Presentation would not discuss investigational compounds and off label treatment modalities
- The topics covered by this presentation were requested by Bio Data organising committee

Links between chronic viral hepatitis, UK HCV research and NASA ?



Personalised medicine?

- **MRC: Stratified Medicine**

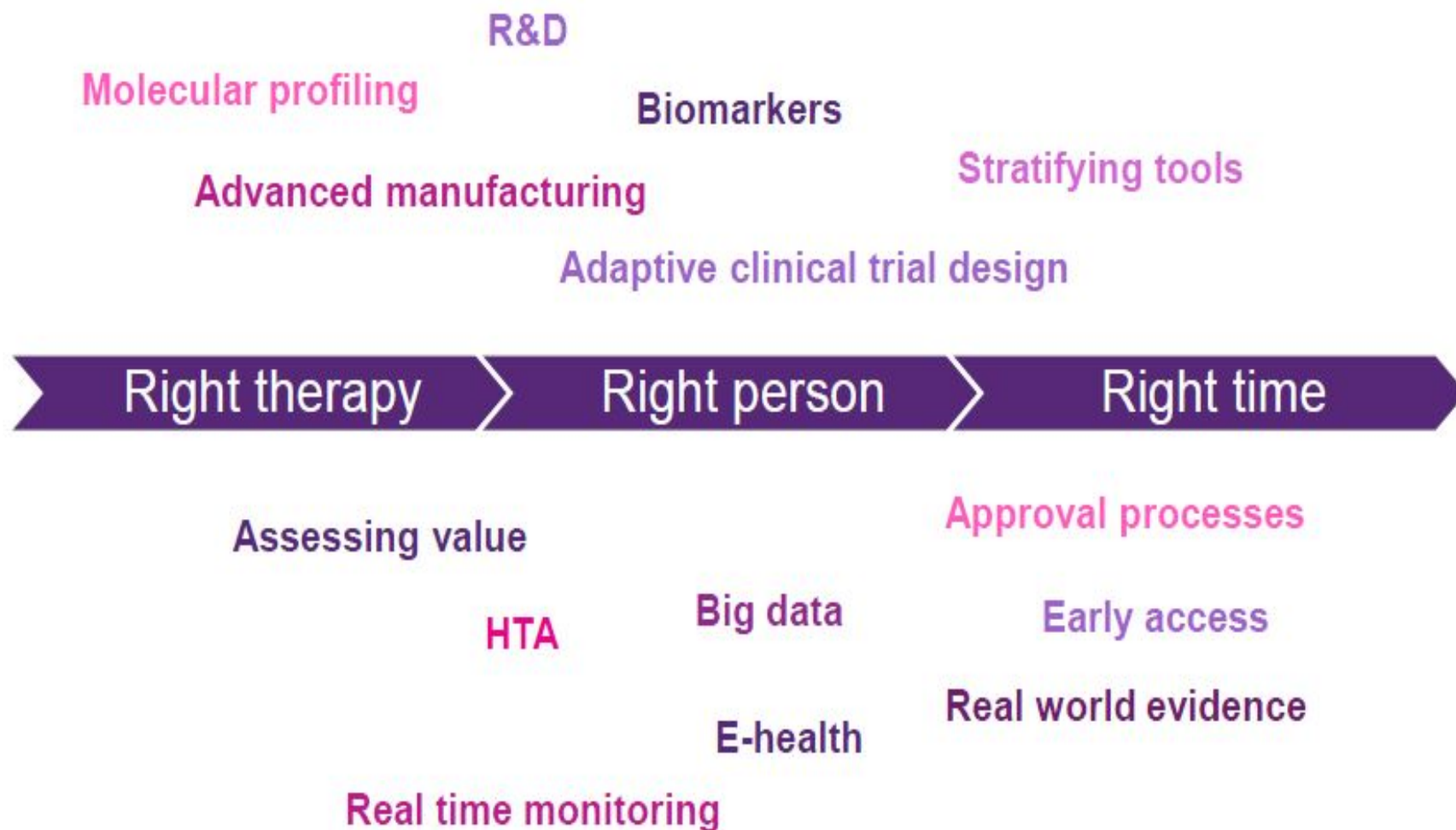
Stratified medicine is based on identifying subgroups of patients with distinct mechanisms of disease, or particular responses to treatments. This allows us to identify and develop treatments that are effective for particular groups of patients. Ultimately stratified medicine will ensure that the right patient gets the right treatment at the right time.

- **NHS: Right Care 2013/14**

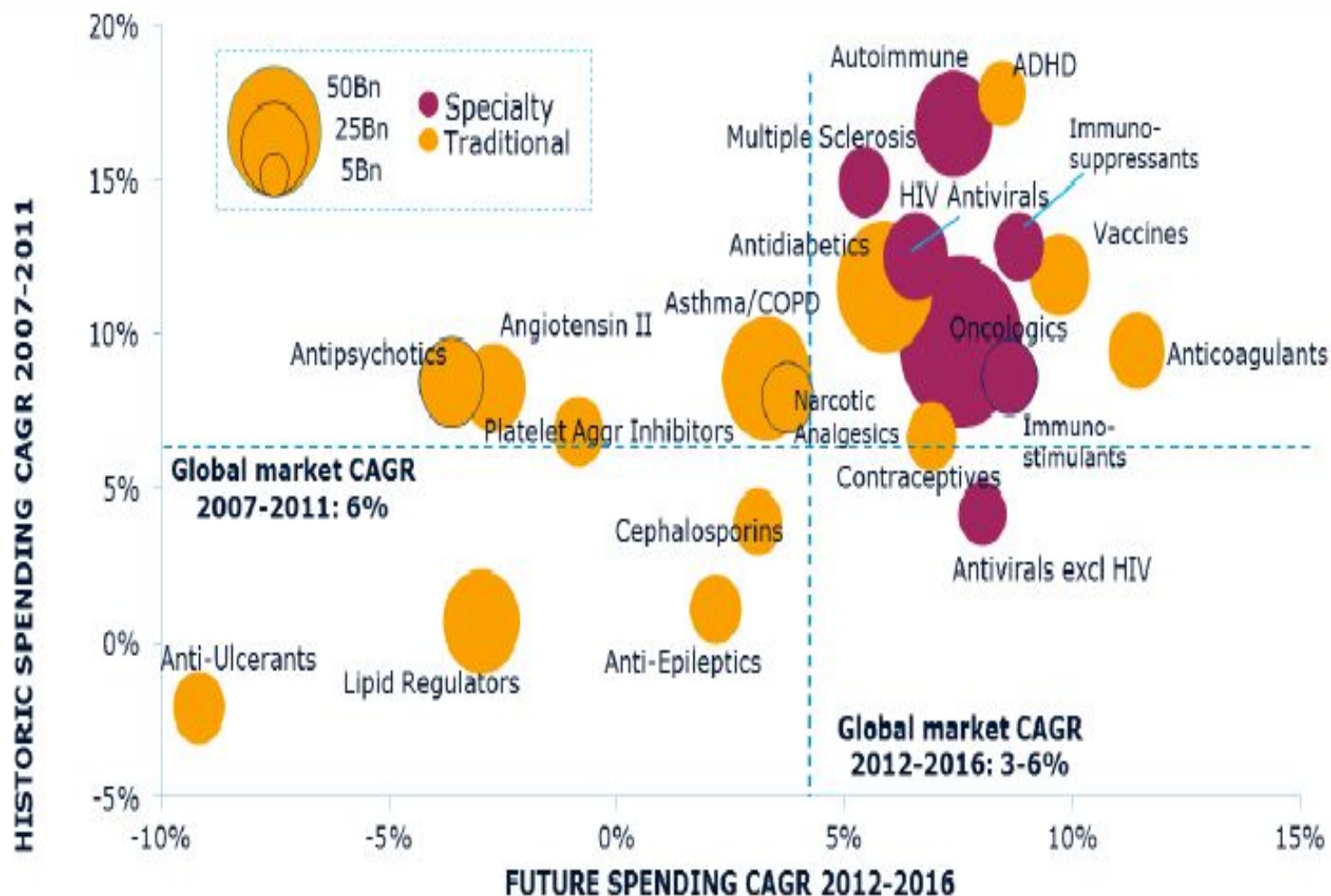
The primary objective for Right Care is to maximise value-the value that the patient derives from their own care and treatment and the value the whole population derives from the investment in their healthcare

Pharma: ” Right treatment for the right patient”

Value chain

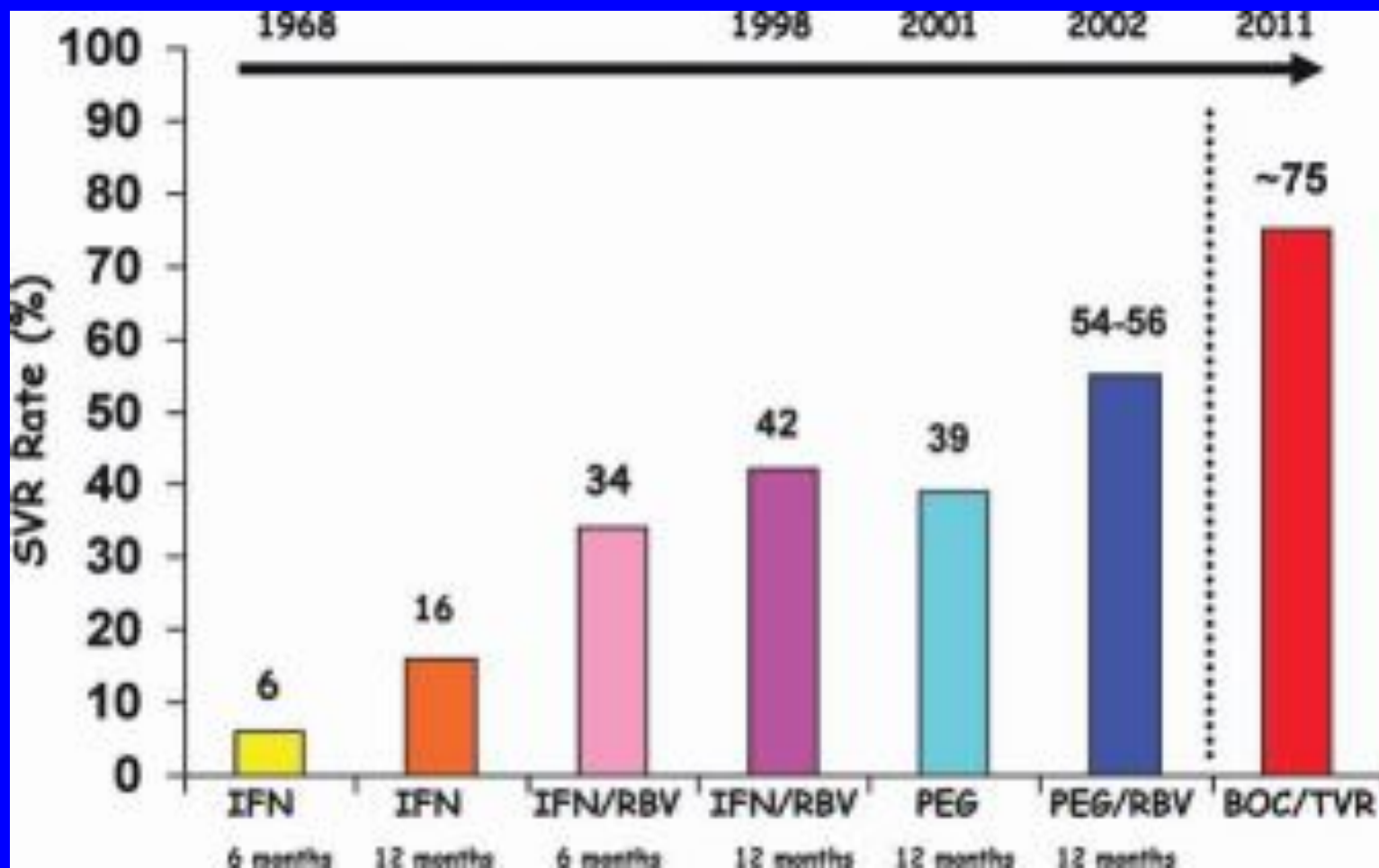


Spending and Growth in Leading Therapy Areas, Global analysis



Future TA growth to be dominated by specialty medicines

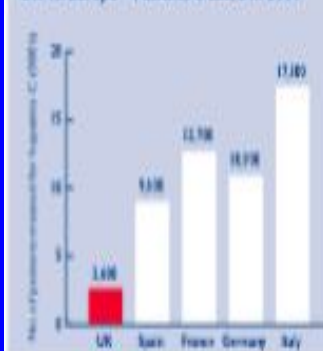
A brief history of HCV treatment



UK-losing the fight against HCV

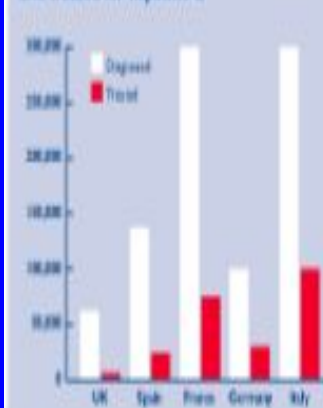


UK vs. Europe - Patients treated in 2004



Source: WHO Data 2004

European figures for patients ever diagnosed and treated for hepatitis C



Of the 67,877 patients who are actually diagnosed as antibody positive in the UK,¹ only one in 20 receives treatment each year.¹ Of the total number infected this treatment rates falls to only 1-2%.¹

This compares to France where 13% of the total number infected receive treatment. In France, 6-12 times as many people diagnosed with hepatitis C are likely to receive treatment than those diagnosed in the UK.¹

The Hepatitis C Trust



BMS-leading liver franchise in 2011

BRISTOL-MYERS SQUIBB R&D PIPELINE



Exploratory Development

Full Development

EGFR/IGFR
Tandem *Adnectin*
Pegdinetanib
(VEGFR-2 *Adnectin*)
Anti-CD70 ADC
JAK2 Inhibitor
IGF-1R Antagonist
SMO Antagonist
IL-21
Anti-KIR
Urelumab
(Anti-CD137)
Notch Inhibitors
Anti-PD1
Anti-CXCR4
Anti-LAG3

PEG-FGF21
11 β HSD Inhibitors
TGR5 Agonist
FGF21-PKE *Adnectin*
GPR119 Agonists

CCR1 Antagonists
Anti-IP10
Anti-CD28
Anti-IL-6
IL-23 *Adnectin*
Anti-IL31
Anti-CD40L
LPA1 Antagonist

LXR Modulators
PCSK9 *Adnectin*
CCR2/5 Antagonists
IKACH Inhibitors
IKur Antagonists

 α -7 Nicotinic Agonist
A β Modulator
Triple Reuptake Inhibitors
Microtubule Stabilizer
Avagacestat
(Gamma Secretase Inhibitor)
GABA/Nicotinic Modulator
CGRP Antagonist

Peginterferon
lambda-1a
Asunaprevir
(NS3 Inhibitor)
NS5B Inhibitor
HIV Attachment Inhibitor
Anti-PD-L1
NRT Inhibitor
HIV Maturation Inhibitor
NS5B Primer Grip Inhibitor
NS5A Second Generation
NS5B Site 1 Inhibitor

Brivanib
Elotuzumab
Necitumumab

Dapagliflozin

Dacatasvir
(NS5A Inhibitor)

Compounds in **Exploratory Development** are in preclinical or early clinical development. **Full Development** compounds are investigational drugs that are in later-stage clinical development or have been submitted to regulatory agencies for approval.

The Ongoing Development for Approved Medicines table

Oncology

Metabolics

Immunoscience

Cardiovascular

Neuroscience

Virology

LB-8



Lo, A.¹, Gardiner, D.², Lawitz, E.³, Martorell, C.⁴, Everson, G.⁵, Ghalib, R.⁶, Reindollar, R.⁷, Rustgi, V.⁸, Wendelburg, P.⁹, Zhu, K.¹⁰, Shah, V.¹¹, Sherman, D.¹², Mo-Phée, F.¹³, Wind-Rotolo, M.¹⁴, Bifano, M.¹⁵, Eley, T.¹⁶, Guo, T.¹⁷, Persson, A.¹⁸, Hinds, R.¹⁹, Grasela, D.²⁰ and Pasquinelli, C.²¹

[illegible]

	Group A EMC-5000 and EMC-70000 n=11 ^a	Group B EMC-50000, EMC-70000, Pylori, ACV n=10 ^b
Genotype 12.9	9	
Median bioactive CD19b titers ^c	6.9 log ₁₀	6.7 log ₁₀
Median bioactive CD19b titers 21 days ^c	<6.1 log ₁₀	<6.1 log ₁₀
RUVP n (%)	7 (63.6%)	6 (60%)
uRUVP n (%)	5 (45.5%)	6 (60%)
cRUVP n (%)	5 (45.5%)	6 (60%) ^d

[illegible][illegible][illegible]

1. **Primary Objective**

- To estimate the proportion of subjects with a measurable HCV RNA at baseline and at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 272, 276, 280, 284, 288, 292, 296, 300, 304, 308, 312, 316, 320, 324, 328, 332, 336, 340, 344, 348, 352, 356, 360, 364, 368, 372, 376, 380, 384, 388, 392, 396, 400, 404, 408, 412, 416, 420, 424, 428, 432, 436, 440, 444, 448, 452, 456, 460, 464, 468, 472, 476, 480, 484, 488, 492, 496, 500, 504, 508, 512, 516, 520, 524, 528, 532, 536, 540, 544, 548, 552, 556, 560, 564, 568, 572, 576, 580, 584, 588, 592, 596, 600, 604, 608, 612, 616, 620, 624, 628, 632, 636, 640, 644, 648, 652, 656, 660, 664, 668, 672, 676, 680, 684, 688, 692, 696, 700, 704, 708, 712, 716, 720, 724, 728, 732, 736, 740, 744, 748, 752, 756, 760, 764, 768, 772, 776, 780, 784, 788, 792, 796, 800, 804, 808, 812, 816, 820, 824, 828, 832, 836, 840, 844, 848, 852, 856, 860, 864, 868, 872, 876, 880, 884, 888, 892, 896, 900, 904, 908, 912, 916, 920, 924, 928, 932, 936, 940, 944, 948, 952, 956, 960, 964, 968, 972, 976, 980, 984, 988, 992, 996, 1000, 1004, 1008, 1012, 1016, 1020, 1024, 1028, 1032, 1036, 1040, 1044, 1048, 1052, 1056, 1060, 1064, 1068, 1072, 1076, 1080, 1084, 1088, 1092, 1096, 1100, 1104, 1108, 1112, 1116, 1120, 1124, 1128, 1132, 1136, 1140, 1144, 1148, 1152, 1156, 1160, 1164, 1168, 1172, 1176, 1180, 1184, 1188, 1192, 1196, 1200, 1204, 1208, 1212, 1216, 1220, 1224, 1228, 1232, 1236, 1240, 1244, 1248, 1252, 1256, 1260, 1264, 1268, 1272, 1276, 1280, 1284, 1288, 1292, 1296, 1300, 1304, 1308, 1312, 1316, 1320, 1324, 1328, 1332, 1336, 1340, 1344, 1348, 1352, 1356, 1360, 1364, 1368, 1372, 1376, 1380, 1384, 1388, 1392, 1396, 1400, 1404, 1408, 1412, 1416, 1420, 1424, 1428, 1432, 1436, 1440, 1444, 1448, 1452, 1456, 1460, 1464, 1468, 1472, 1476, 1480, 1484, 1488, 1492, 1496, 1500, 1504, 1508, 1512, 1516, 1520, 1524, 1528, 1532, 1536, 1540, 1544, 1548, 1552, 1556, 1560, 1564, 1568, 1572, 1576, 1580, 1584, 1588, 1592, 1596, 1600, 1604, 1608, 1612, 1616, 1620, 1624, 1628, 1632, 1636, 1640, 1644, 1648, 1652, 1656, 1660, 1664, 1668, 1672, 1676, 1680, 1684, 1688, 1692, 1696, 1700, 1704, 1708, 1712, 1716, 1720, 1724, 1728, 1732, 1736, 1740, 1744, 1748, 1752, 1756, 1760, 1764, 1768, 1772, 1776, 1780, 1784, 1788, 1792, 1796, 1800, 1804, 1808, 1812, 1816, 1820, 1824, 1828, 1832, 1836, 1840, 1844, 1848, 1852, 1856, 1860, 1864, 1868, 1872, 1876, 1880, 1884, 1888, 1892, 1896, 1900, 1904, 1908, 1912, 1916, 1920, 1924, 1928, 1932, 1936, 1940, 1944, 1948, 1952, 1956, 1960, 1964, 1968, 1972, 1976, 1980, 1984, 1988, 1992, 1996, 2000, 2004, 2008, 2012, 2016, 2020, 2024, 2028, 2032, 2036, 2040, 2044, 2048, 2052, 2056, 2060, 2064, 2068, 2072, 2076, 2080, 2084, 2088, 2092, 2096, 2100, 2104, 2108, 2112, 2116, 2120, 2124, 2128, 2132, 2136, 2140, 2144, 2148, 2152, 2156, 2160, 2164, 2168, 2172, 2176, 2180, 2184, 2188, 2192, 2196, 2200, 2204, 2208, 2212, 2216, 2220, 2224, 2228, 2232, 2236, 2240, 2244, 2248, 2252, 2256, 2260, 2264, 2268, 2272, 2276, 2280, 2284, 2288, 2292, 2296, 2300, 2304, 2308, 2312, 2316, 2320, 2324, 2328, 2332, 2336, 2340, 2344, 2348, 2352, 2356, 2360, 2364, 2368, 2372, 2376, 2380, 2384, 2388, 2392, 2396, 2400, 2404, 2408, 2412, 2416, 2420, 2424, 2428, 2432, 2436, 2440, 2444, 2448, 2452, 2456, 2460, 2464, 2468, 2472, 2476, 2480, 2484, 2488, 2492, 2496, 2500, 2504, 2508, 2512, 2516, 2520, 2524, 2528, 2532, 2536, 2540, 2544, 2548, 2552, 2556, 2560, 2564, 2568, 2572, 2576, 2580, 2584, 2588, 2592, 2596, 2600, 2604, 2608, 2612, 2616, 2620, 2624, 2628, 2632, 2636, 2640, 2644, 2648, 2652, 2656, 2660, 2664, 2668, 2672, 2676, 2680, 2684, 2688, 2692, 2696, 2700, 2704, 2708, 2712, 2716, 2720, 2724, 2728, 2732, 2736, 2740, 2744, 2748, 2752, 2756, 2760, 2764, 2768, 2772, 2776, 2780, 2784, 2788, 2792, 2796, 2800, 2804, 2808, 2812, 2816, 2820, 2824, 2828, 2832, 2836, 2840, 2844, 2848, 2852, 2856, 2860, 2864, 2868, 2872, 2876, 2880, 2884, 2888, 2892

Study Design

Group A: $ENG = 70000 \pm 2$, $ENG = 67000 \pm 1000$

Group B: $ENG = 70000 \pm 2$, $ENG = 67000 \pm 1000$, $PAFT = 100 \pm 5$

2-week duration of therapy

Follow-up: up to 48 weeks post-treatment

• 5140 ± 7000 100 ± 5 100 ± 5 100 ± 5 100 ± 5
• 5140 ± 7000 100 ± 5 100 ± 5 100 ± 5 100 ± 5
• $PAFT = 100 \pm 5$ 100 ± 5 100 ± 5 100 ± 5 100 ± 5
• 100 ± 5 100 ± 5 100 ± 5 100 ± 5 100 ± 5
• 100 ± 5 100 ± 5 100 ± 5 100 ± 5 100 ± 5

<p>Key Inclusion and Exclusion Criteria</p> <p>Inclusion Criteria</p> <ul style="list-style-type: none"> • Chronic ICU bedrock, geriatric • Well recognized > 24 hours in ICU bed • Received 12 months of chronic pain medication • ICU bedrock > 12 months • Received 12 months of chronic pain medication <p>Exclusion Criteria</p> <ul style="list-style-type: none"> • ICU bedrock > 24 hours in ICU bed • Received 12 months of chronic pain medication • ICU bedrock > 12 months • Received 12 months of chronic pain medication 	<p>Key Inclusion and Exclusion Criteria</p> <p>Inclusion Criteria</p> <ul style="list-style-type: none"> • ICU bedrock > 24 hours in ICU bed • Received 12 months of chronic pain medication • ICU bedrock > 12 months • Received 12 months of chronic pain medication <p>Exclusion Criteria</p> <ul style="list-style-type: none"> • ICU bedrock > 24 hours in ICU bed • Received 12 months of chronic pain medication • ICU bedrock > 12 months • Received 12 months of chronic pain medication
--	--

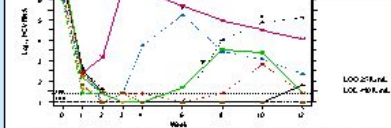
APC1 flag-tagged cells were treated with 100 nM of APC1 inhibitor, and the cells were harvested 24 h after treatment. The cells were then lysed, and the lysates were immunoprecipitated with anti-APC1 antibody. The immunoprecipitates were then immunoblotted with anti-APC1 antibody. The results are shown in Figure 1. The results show that the APC1 inhibitor treatment significantly increased the levels of APC1 in the cells.

	Group A n=115	Group B n=105
Medication use ^a	9	56.5
Medication ^b	90	48
Place of delivery (n=1)		
Home	18.25	7.705
NICU/Neonatal Intensive Care Unit	21.45	21.205
Hospital	69.30	71.09
Medication within 1 CVR 2.0 risk adjusted ^c		
CV 2.0 group (n=15)		6.7
1.5	18.25	
1G	21.45	11.05
Mean baseline NLT (1.4)	70.5	57.9

Vind oggi l'aspirazione		
	Group A n=10 (10%)	Group B n=10 (10%)
Medicine 1 CV R14, deinde ne vive 2 (Medic1),	<1	<1
CV14 ne vixit,	7 (70%)	6 (60%)
deinde ne vixit,	3 (30%)	4 (40%)
CV14 ne vixit,	5 (50%)	3 (30%)
CV14 ne vixit,	5 (50%)	4 (40%)
Total medic1 deinde ne vixit	6 (60%)	0

* Complete membership is required in the following groups to be eligible for the HEN FPM Award:
 1. The subject group 8.1.1 [the subject group HEN FPM 7.8.1.1], however, membership of the HEN FPM.com website is not a requirement.
 2. Membership of any of the groups in HEN FPM 8.1.1, however, membership of any of the groups in HEN FPM 7.8.1.1 is not a requirement for eligibility.

HCV RNA Urdnung by Subject Group A



1. Viralbreakthrough occurs only in group B subjects with genotype 12. No more observed in either 24 week 1 or 24 week 24 week 12 or therapy
 2. Viralbreakthrough occurs with higher baseline HCV RNA levels
 3. Subjects with viralbreakthrough has higher HCV RNA at their treatment
 4. Pretherapy genotype had no effect on subjects with or without viralbreakthrough. Indicate a correlation of genotype 12 with HCV RNA at baseline
 5. Pretherapy genotype had no effect on subjects with or without viralbreakthrough. Indicate a correlation of genotype 12 with HCV RNA at baseline

Figure 1 is a line graph showing LOD score curves for 12 chromosomes. The y-axis is labeled 'Log₁₀ P < 0.001' and ranges from 1 to 7. The x-axis is labeled 'Chromosome' and ranges from 0 to 12. A solid line represents the LOD score with RILs, and a dashed line represents the LOD score with bulked segregant analysis. A horizontal dotted line at approximately 1.3 indicates the significance threshold. Chromosome 12 shows a significant peak labeled 'A'.

- No viral breakthrough occurred in group B
- 100% of all lesions were treatable by week 6 or therapy
- Virologic control was maintained through week 12 in all subjects
- One subject with HCV RNA <25 IU/mL at week 12 relapsed above 15 IU/mL was treatable with treatment reinitiation

Subject	Peak ICU RHO Photo Reactivity PpP/RHO	Outcome at Week 12 Grade
1	661	LO
2	136	>25 React
3	6650*	LO
4	7129	27 React
5	16290	>25 React
6	12711*	60% React

■ I-CD Rhd increases in all patients after the section of pectinase to the 2-3rd subgingival space;
 + patient has I-CD Rhd +21mm, 2x of the neck, 1.2mm hole

Shawby Table 1 Thermodynamic Data						
Sub P. Enzyme	ENE-670002				ENE-700002	
	Exp. 1 ^a				Exp. 2 ^b	
	Group A n (cell %)	Group B n (cell %)	Group A n (cell %)	Group B n (cell %)	Group A n (cell %)	Group B n (cell %)
C ₁₂ -phosphatidyl GAPC C16	18/20 (90.0%)	18/40 (45.0%)	10/20 (50.0%)	14/20 (70.0%)	14/20 (70.0%)	14/20 (70.0%)
T ₁₀ -PMS	21/21 (100%)	21/21 (100%)	21/21 (100%)	21/21 (100%)	21/21 (100%)	21/21 (100%)
Adenosine 3',5'-bisphosphate GAPC C16	6/20 (30.0%)	6/20 (30.0%)	6/20 (30.0%)	6/20 (30.0%)	6/20 (30.0%)	6/20 (30.0%)
C ₁₂ -phosphatidyl GAPC C16	18/20 (90.0%)	18/40 (45.0%)	10/20 (50.0%)	14/20 (70.0%)	14/20 (70.0%)	14/20 (70.0%)

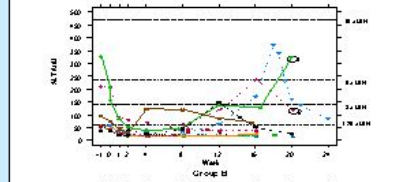
[illegible]

- Exposure to long-term conditions (asthma, diabetes, heart disease) is linked to poorer health outcomes
- Exposure to long-term conditions with those exposure to health vulnerability (Macken et al, 2016) p. 275

Group A	Group B	Group C	Total
10	10	10	30

[illegible][illegible][illegible]

ALI by Group Year Item Group A



Week

Other Identity Forming
= Number of subjects who Graded-Laboratory, also enrolled in class:

<ul style="list-style-type: none"> • 1 <i>Edwardsiella iberopneumoniae</i> in Group B • 2 <i>WBC's</i>, both in Group B • 3 <i>GLT's</i> in Groups 2 and 3 in Group B • 4 <i>GLT's</i> in Group 2 	<ul style="list-style-type: none"> • 1 <i>Edwardsiella iberopneumoniae</i> in Group B • 1 <i>Upate</i> in Group 6 • 1 <i>Sevize</i> in Group 6
---	---

- Pluralis

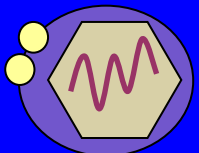
CONCLUSIONS

- Sono osservate nell'8-20 giorni dopo il parto
- SGA: <1000g e più SGA: <600g in correlazione con preeclampsia, diabete, ipertensione, anemia, parto prematuro
- SGA: il 10-15% delle nascite, aumentano con l'età della madre, diabete, ipertensione, anemia, parto prematuro
- Sono associate con: insufficienza placentare, basso peso alla nascita

[illegible]

HCV Research UK

- Funded by the Medical Research Foundation in 2011, consists of
 - A cohort of patients ($n > 10,000$)
 - A database
 - A biobank
 - By end 2014 (400 patients per month), with 10 year follow-up
- i.e. is not an end in itself but a resource for all to access

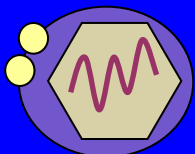


HCV Research UK



The cohort: Who?

- Clinic attenders with evidence of HCV infection
 - Only exclusion is inability to consent
 - At all stages of disease/management
- Targeted specific subgroups
 - Spontaneous resolvers
 - Post-therapy SVR



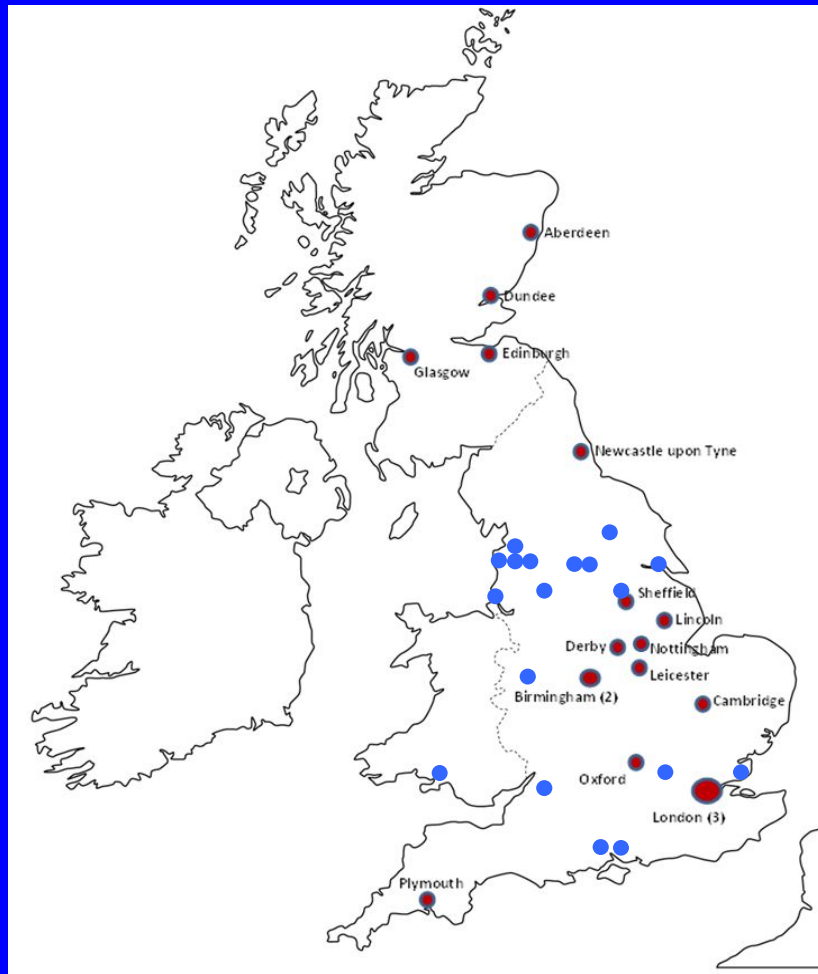
HCV Research UK



The cohort: Where?

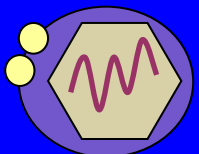
Original 18

Glasgow
Aberdeen
Dundee
Edinburgh
Newcastle upon Tyne
Sheffield
Nottingham
Lincoln
Derby
Birmingham
B'ham Children's
Leicester
Cambridge
Oxford
London x3
Plymouth

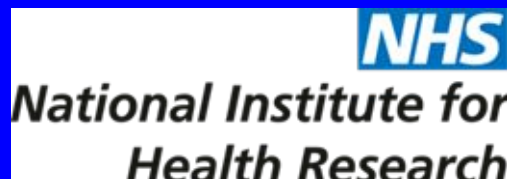


21 New or Potential Sites

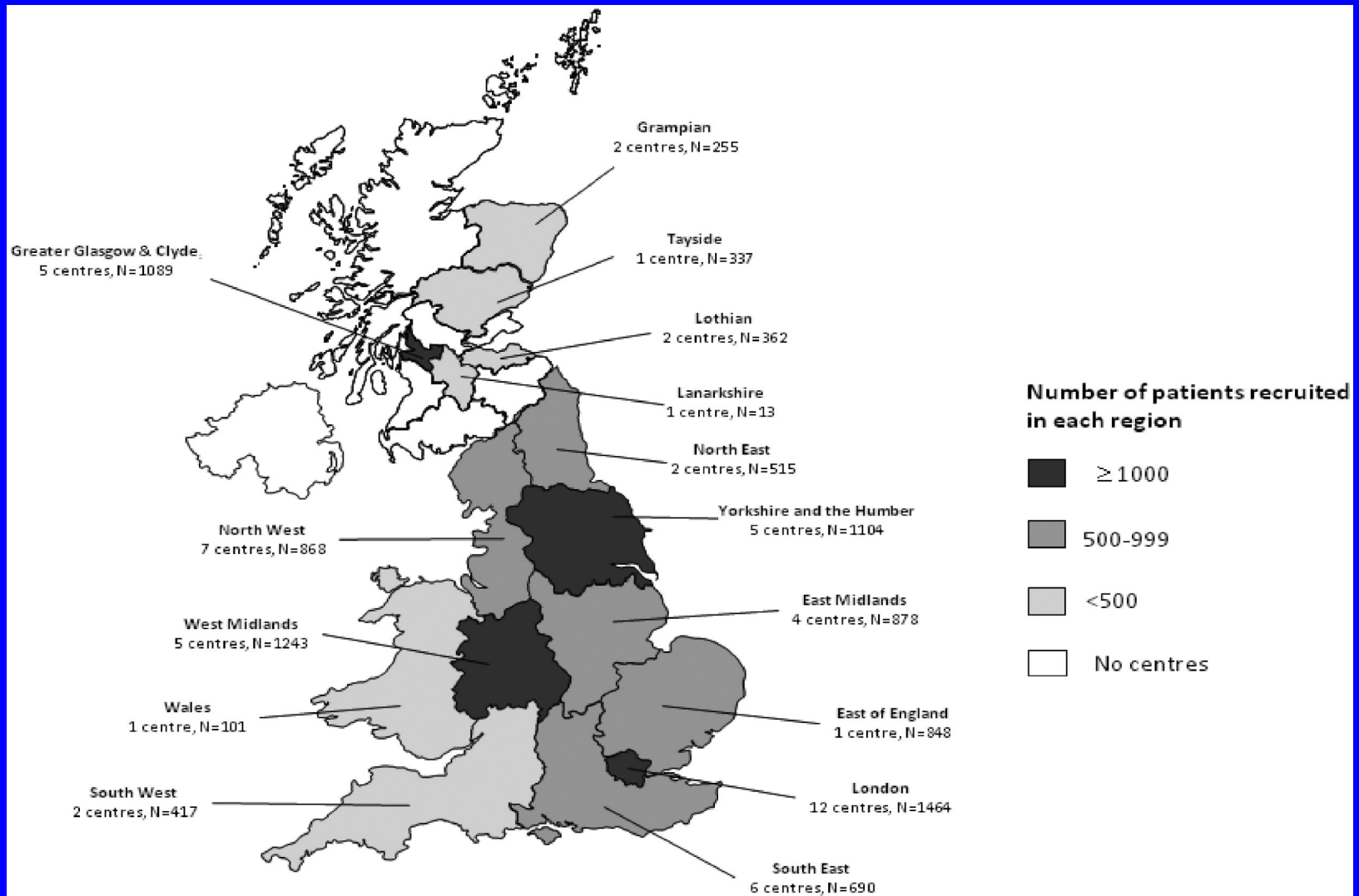
Manchester x2
Liverpool
Leeds
Southampton
Wycombe
Middlesbrough
Hull
Bradford
Preston
Blackburn
Lancaster
Blackpool
Shrewsbury
Bristol
Portsmouth
Lewisham
Southend
Birmingham Heartlands
St Georges
Kings & Leeds children



HCV Research UK

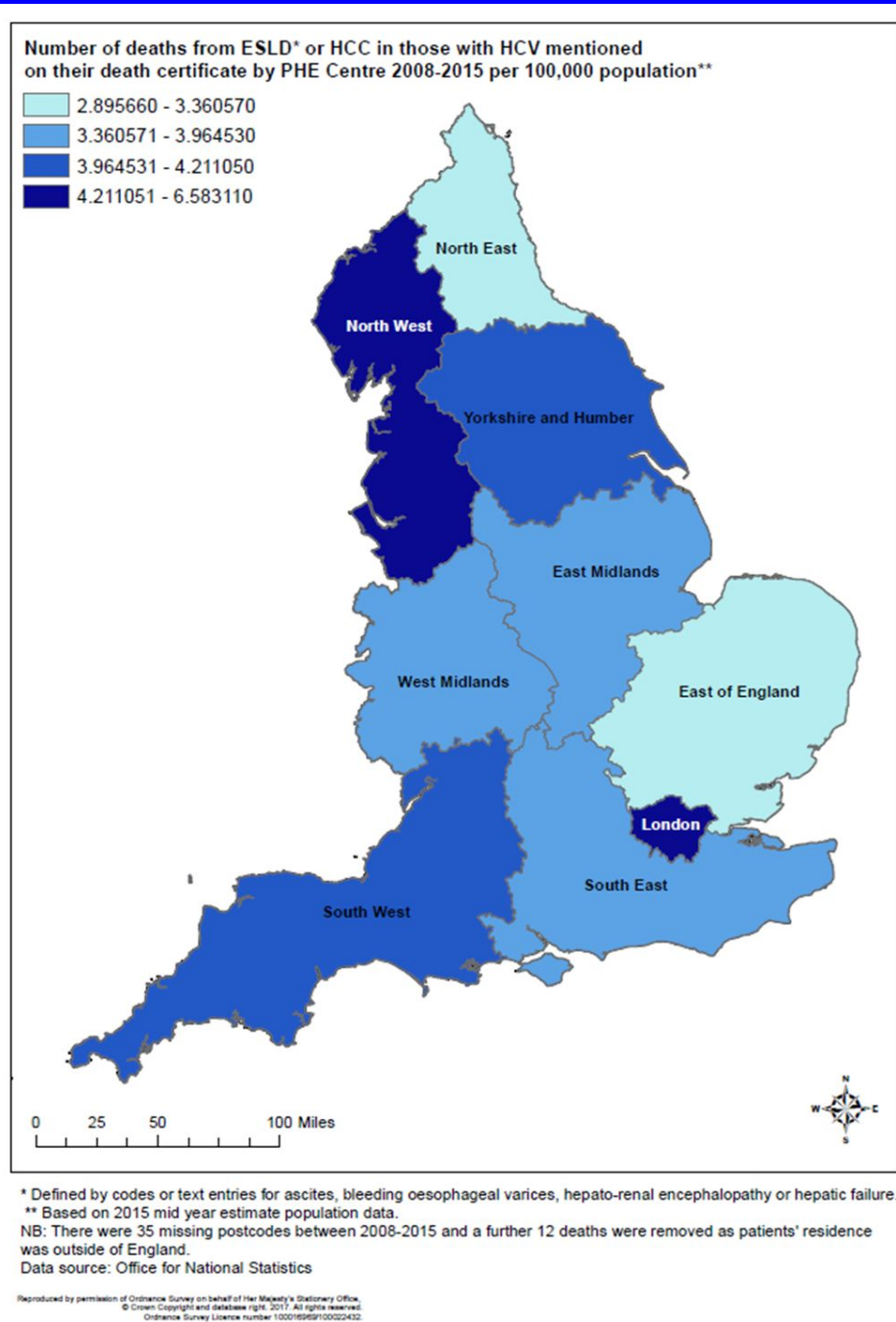


Number of patients recruited in different regions



From: Cohort Profile: The Hepatitis C Virus (HCV) Research UK Clinical Database and Biobank
Int J Epidemiol. Published online February 27, 2017. doi:10.1093/ije/dyw362

Rate of deaths from ESLD HCC in HCV individuals by PHE Centre, 2008–15 per 100,000 population





Stratified Medicine to Optimise treatment for Patients with HCV infection

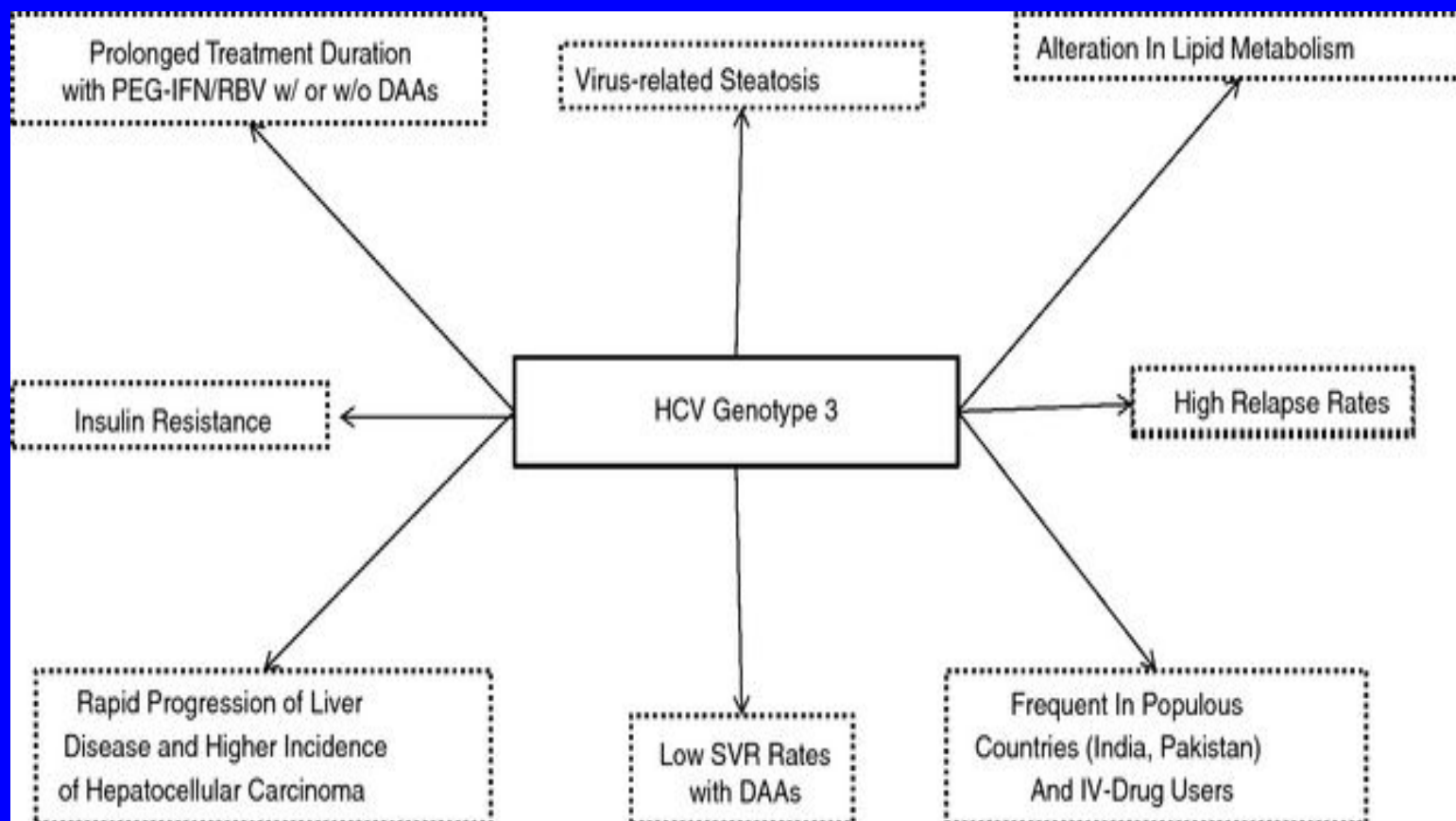
Ellie Barnes



Broad aims of STOP-HCV

- Stratification to develop prognostic risk prediction models to identify patients that will (or will not) benefit from different treatment regimes
- Identify mechanisms that underpin stratification
- Strategic emphasis on:
 - HCV genotype-3 infection
 - Difficult to treat patients: Cirrhosis and HIV co-infection.
 - Development of HCC and negative clinical outcomes

HCV genotype 3 – the new treatment challenge



Industrial Partnership

- Gilead Sciences Ltd
 - Sofosbuvir/Rib vs IFN/sofosbuvir/Rib
- BMS,
 - On-going:
- Merck (PA, USA)
 - Gene expression profiling and response to Rx
- Merck (NJ, USA)
 - Predictors of response to NS5a inhibitors
- Janssen diagnostics
 - Fibrosis/HCC diagnostics
- Medivir
 - In vitro characterisation of naturally-occurring RAVs
- OncImmune
 - AutoAb to predict HCC
- Conatus
 - Biopsy mRNA as predictor of ↑ fibrosis
- United Therapeutics
 - Proteomic markers of fibrosis progression

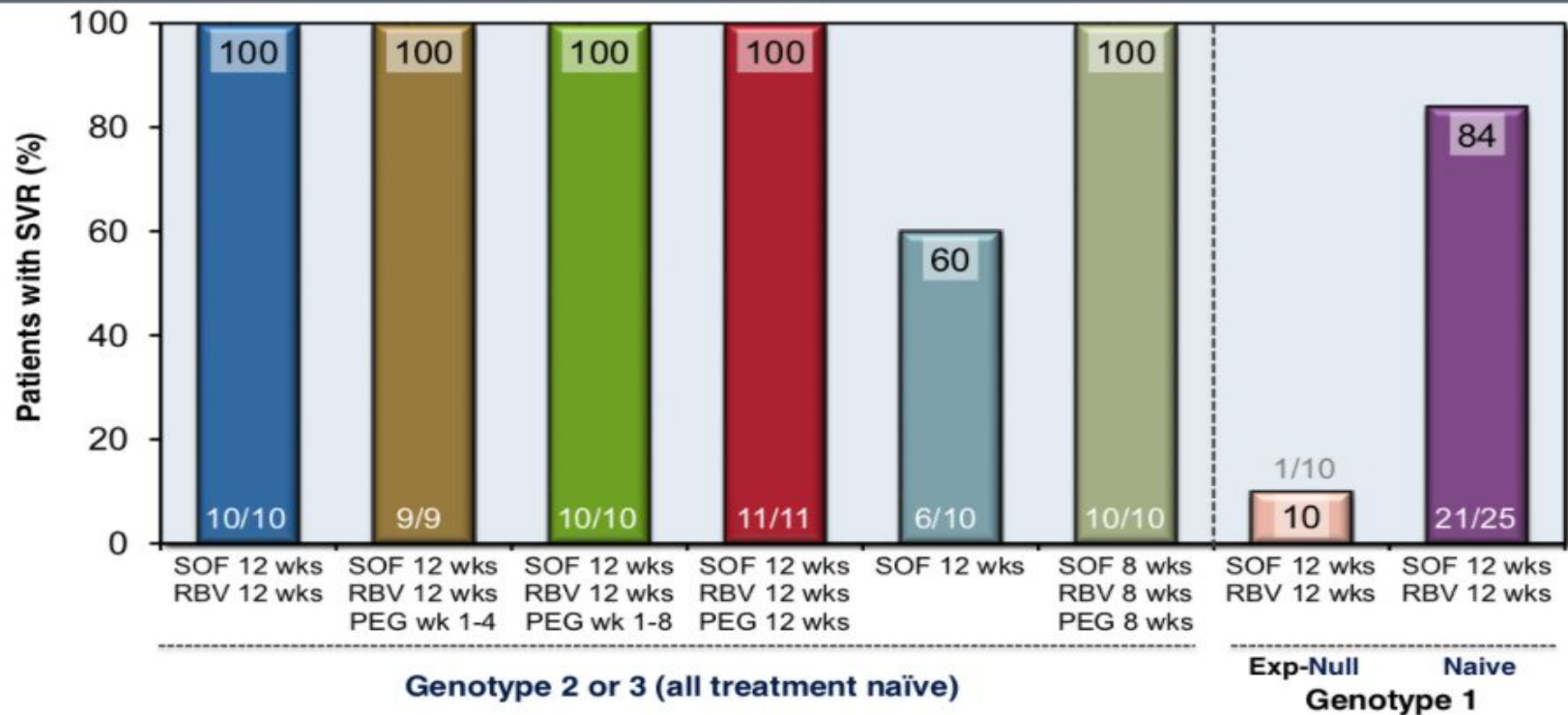
New Developments

- Boson trial (Gilead)
 - PEG/Sof/RV in g3
- Compassionate use
 - Sof (£35k per patient, 500 patients £18m) + Daclatasvir/Ledispavir
- HCC biobank (CRUK)

The beginning of HCV end

Sofosbuvir and Ribavirin +/- Peginterferon in GT 1-3 ELECTRON Trial (Arms 1-8): Results

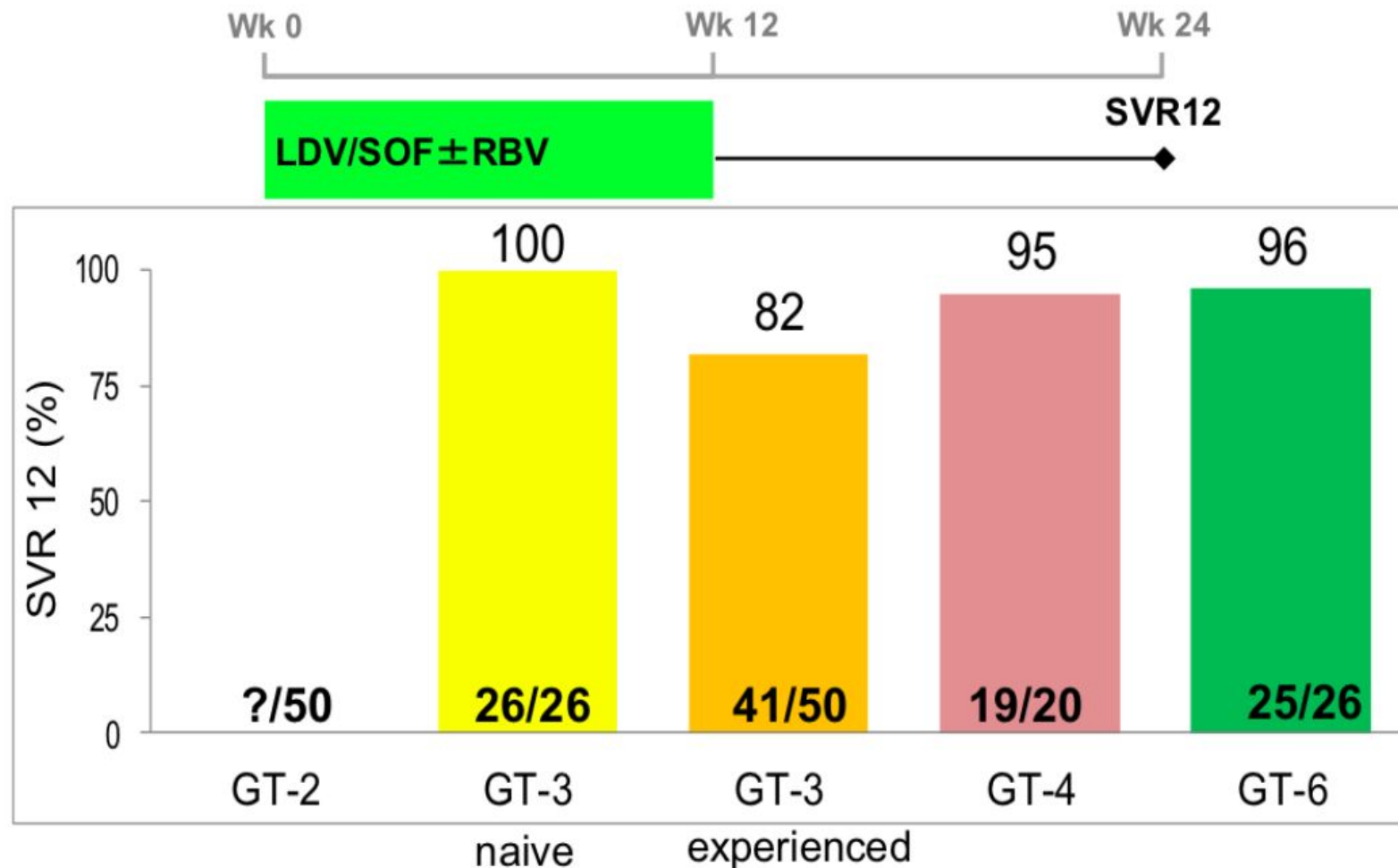
ELECTRON: SVR 12, by Treatment Regimen



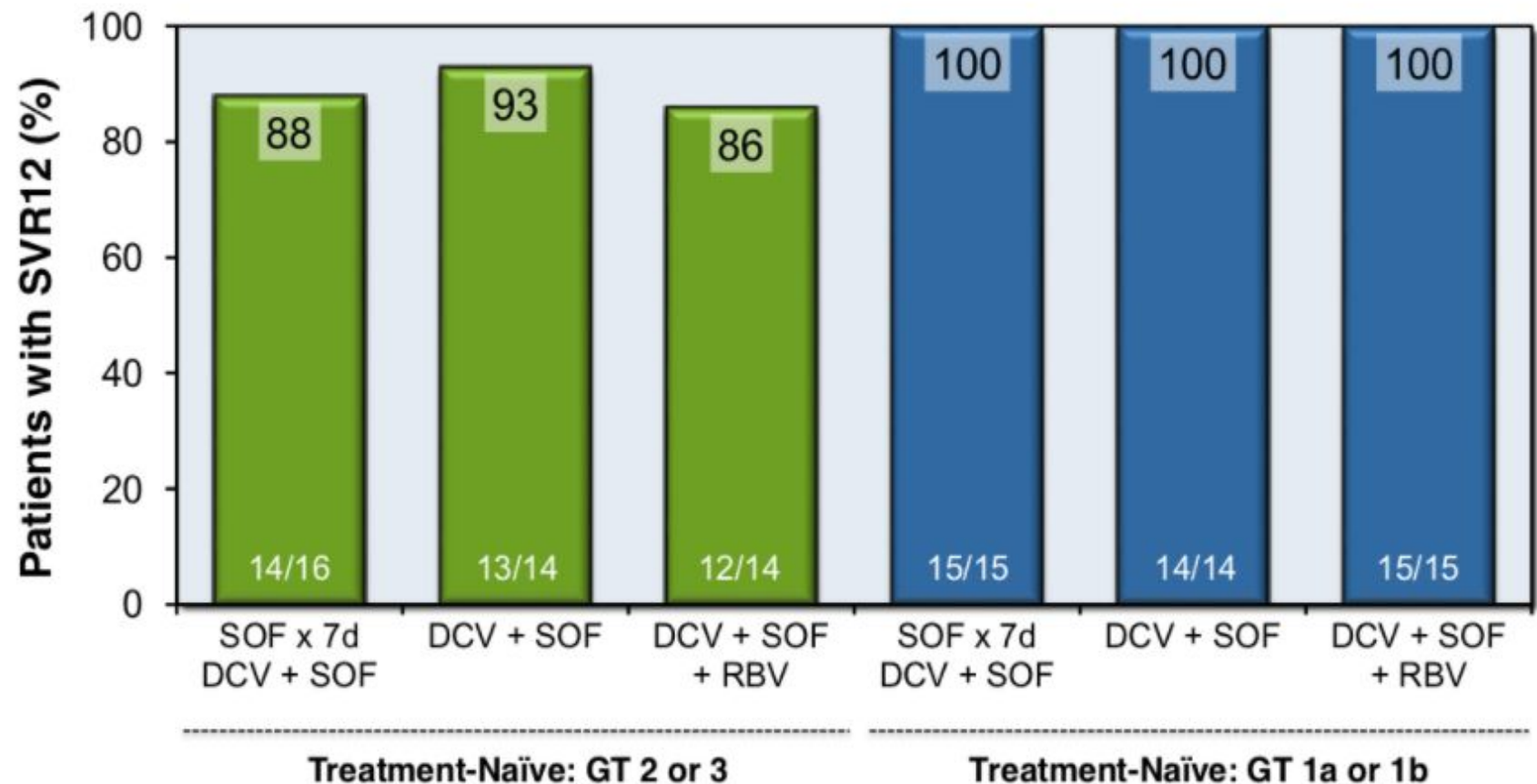
Source: Gane EJ, et al. N Engl J Med. 2013;368:34-44.

Electron 2

Phase 2, open-label studies of LDV/SOF±RBV for 12 weeks



Daclatasvir + Sofosbuvir +/- Ribavirin for HCV GT 1-3 A1444-040 Treatment-Naïve 24 Week Rx: Results



DCV = daclatasvir; SOF = sofosbuvir; RBV = ribavirin

Source: Sulkowski MS, et al. N Engl J Med. 2014;370:211-21.

DCV Early Access Programs in Europe

A multicenter, treatment protocol for the compassionate use of DCV + SOF (+/- RBV) (under Art. 83)

- Population – Patients at high risk of decompensation or death within 12 months if left untreated (in alignment with CHMP opinion)
- N = 300 pts
- Across Europe
- Only DCV will be provided
- Safety & Additionally efficacy data generated during the follow-up collected



Named Patient Program in the UK

- 28 approved patients
- Across 10 UK sites

France - ATU Cohort (CUP)

- Population: Patients with CHC with high risk of decompensation or death within 12 months if left untreated (including peri-transplant situation)
- Regimen: DCV + SOF
- Estimated number of patients: 200 pts

NPP

- Population – Life expectancy < 12 months
- Across Europe
- DCV in multiple combinations (ASV/SMV/SOF)
- Safety information to be reported

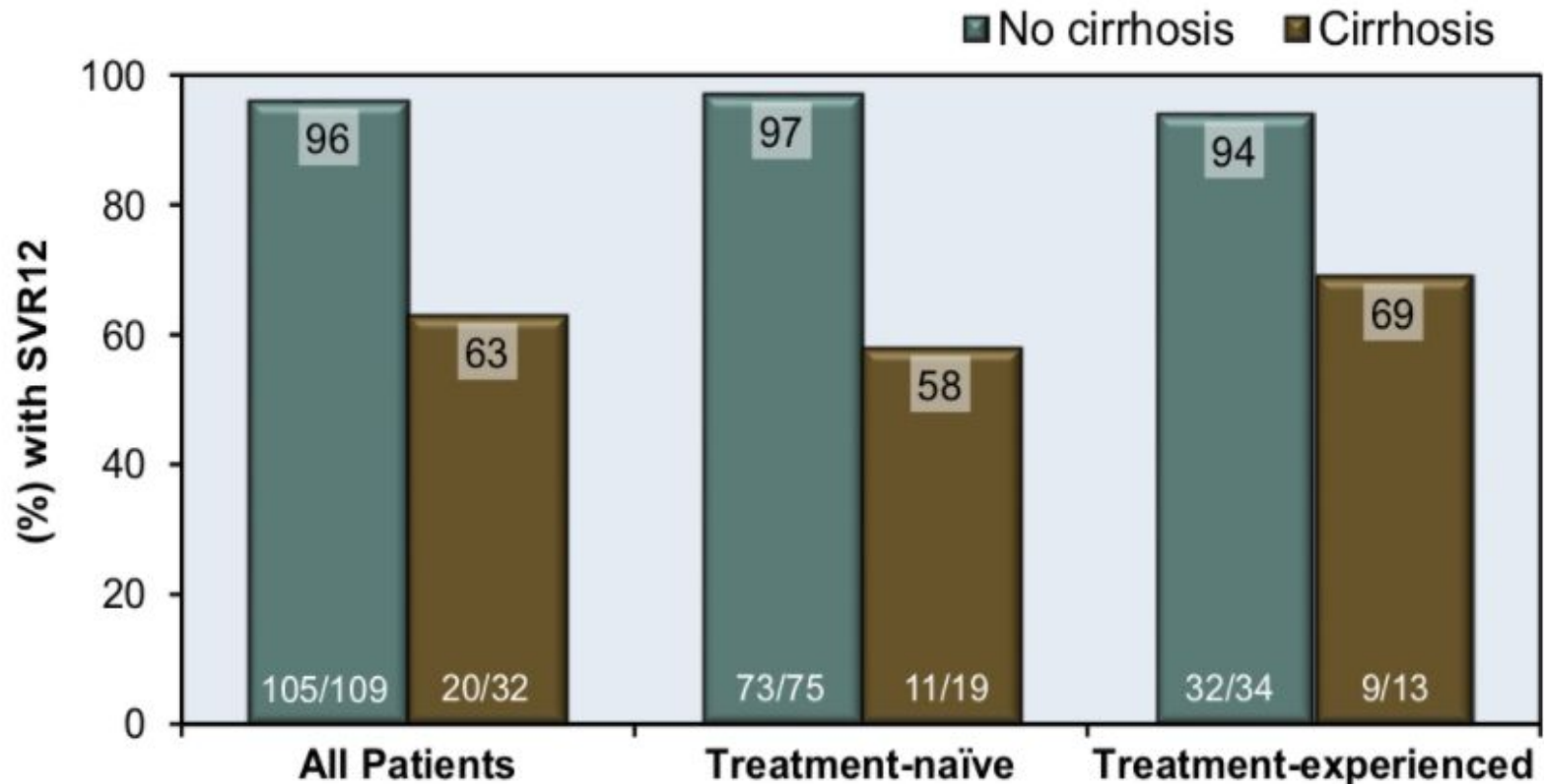
BMS vs FDA- Q4 2014

- In November, the FDA issued a Complete Response Letter regarding the New Drug Application (NDA) for daclatasvir, an NS5A complex inhibitor, in combination with other agents for the treatment of hepatitis C (HCV). The initial daclatasvir NDA focused on its use in combination with asunaprevir, an NS3/4A protease inhibitor. Given the withdrawal of asunaprevir in the U.S. by Bristol-Myers Squibb in October, the FDA is requesting additional data about daclatasvir in combination with other antiviral agents for the treatment of HCV. Daclatasvir is marketed as *Daklinza* in Japan and the European Union.
- In November, the company announced results from the landmark ALLY trial investigating a ribavirin-free 12-week regimen of daclatasvir in combination with sofosbuvir in genotype 3 HCV patients, a patient population that has emerged as one of the most difficult to treat. The data, which showed sustained virologic response 12 weeks after treatment (SVR12) in 90% of treatment-naïve and 86% of treatment-experienced patients, were presented at the annual meeting of the American Association for the Study of Liver Diseases (AASLD) in Boston.

Daclatasvir + Sofosbuvir for HCV GT 3

ALLY-3 Trial: Results

ALLY-3: SVR12, by Cirrhosis Status

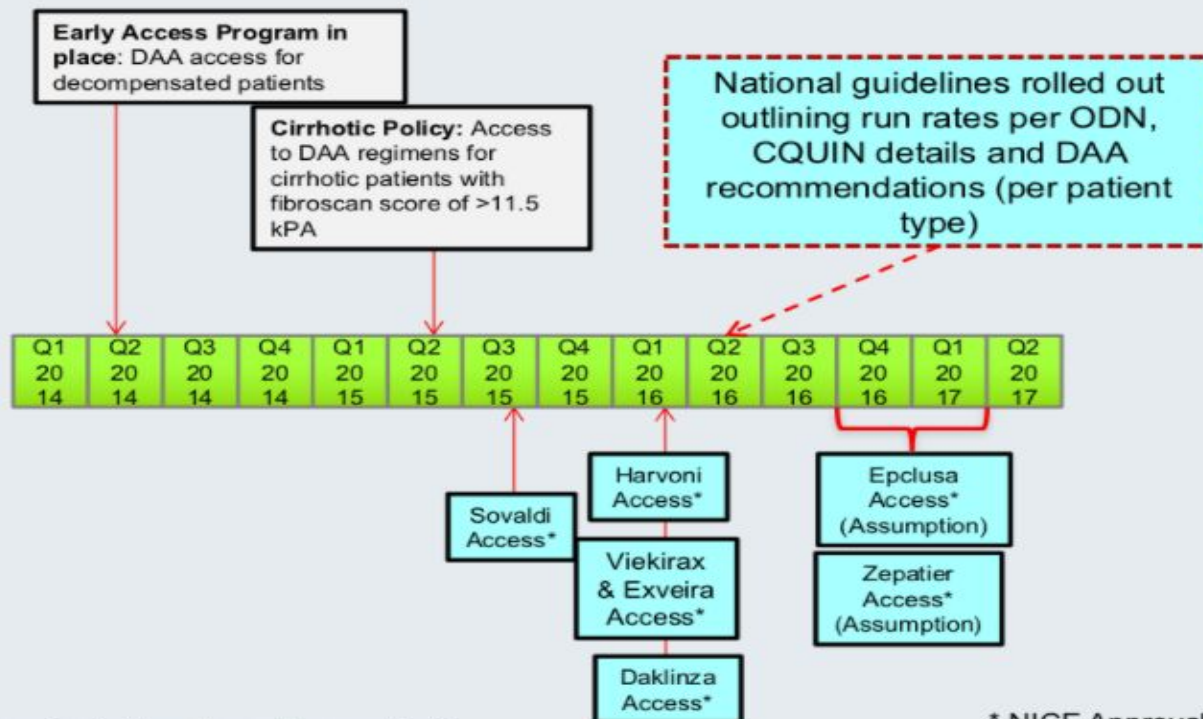


Note: 11 had missing or inconclusive findings for cirrhosis and not included in denominators

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

NHSE comes to the rescue

Summary of DAA Access in England



Note: All points are were approximated based on guidance publication

* NICE Approval

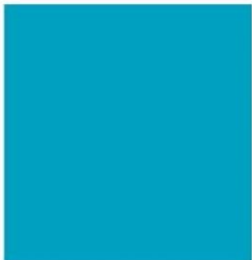
References:

1. Interim Clinical Commissioning Policy Statement Available at: <https://www.england.nhs.uk/wp-content/uploads/2014/04/sofosbuvir-pol-stat.pdf> - Accessed August 2016
2. Clinical Commissioning Policy Statement: Treatment of chronic Hepatitis C in patients with cirrhosis Available at: <https://www.england.nhs.uk/wp-content/uploads/2016/06/hep-c-cirrhosis-policy-statement-0615.pdf> - Accessed August 2016

NHSE commissioning statements



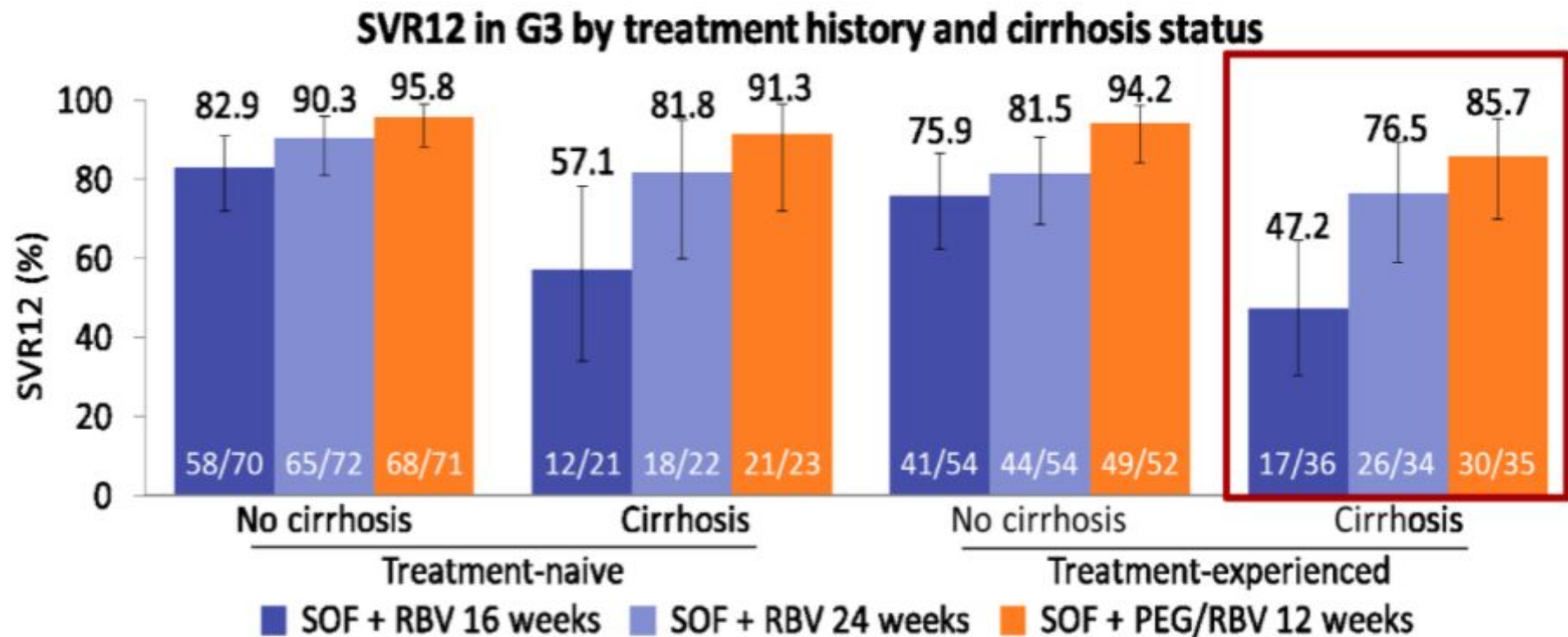
**Interim Clinical Commissioning
Policy Statement:**
**Sofosbuvir + Daclatasvir/Ledipasvir
+/- Ribivirin for defined patients with
Hepatitis C**
April 2014
Reference: NHS ENGLAND A02/PS/b



**Clinical Commissioning Policy
Statement:**
**Treatment of chronic Hepatitis C in
patients with cirrhosis**

Reference: NHS England B07/P/a

BOSON trial



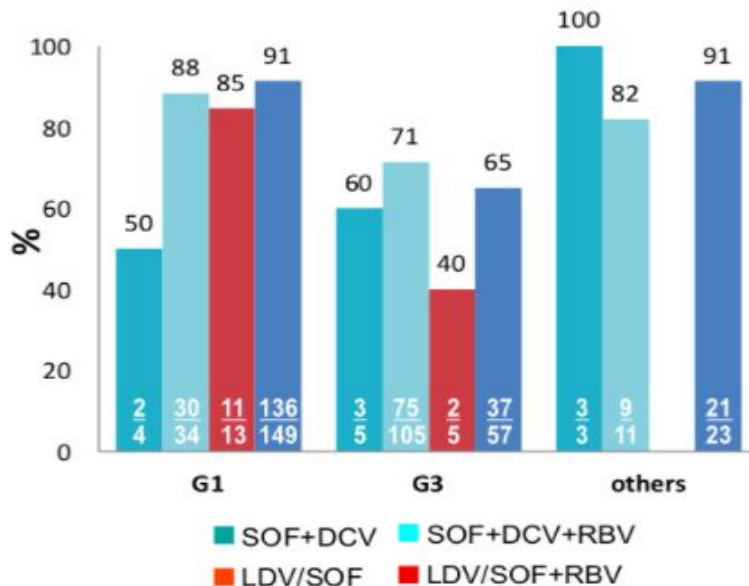
EAP first cohort at EASL 2015

English Access Program

SOF+DCV±RBV or LDV/SOF±RBV for 12 weeks in Patients with Advanced HCV Cirrhosis

SVR12

For patients with decompensated cirrhosis
N=409 – Overall SVR = 80.4%



Adverse Events – first 6 months (3 months Rx, 3 months post-Rx)

Event, n (%)	All Treated (n=409)	Untreated (n=261)
Deaths	13 (3.2%)	15 (5.7%)
Decompensation	72 (17.6%)	73 (28.0%)*
New HCC	19 (4.6%)	21 (8.0%)
Sepsis	27 (6.6%)	15 (5.7%)
New OLT	27 (6.6%)	10 (3.8%)
Hospital admissions	133 (32.5%)	83 (31.8%)
MELD worsening >2	94 (23.0%)	99 (37.9%)*
Total adverse outcomes	213 (52.1%)	166 (63.6%)*

*P < 0.05 between treated and untreated

SOF-based treatment was associated with short term improvements in clinical outcomes

24/07/2015-FDA approves DCV



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206843

NDA APPROVAL

Bristol-Myers Squibb Company
Attention: Marianne Frost
Director, Global Regulatory, Safety & Biometrics - US
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Frost:

Please refer to your New Drug Application (NDA), received March 31, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DAKLINZA (daclatasvir) tablets 30 and 60 mg.

We acknowledge receipt of your amendments dated:

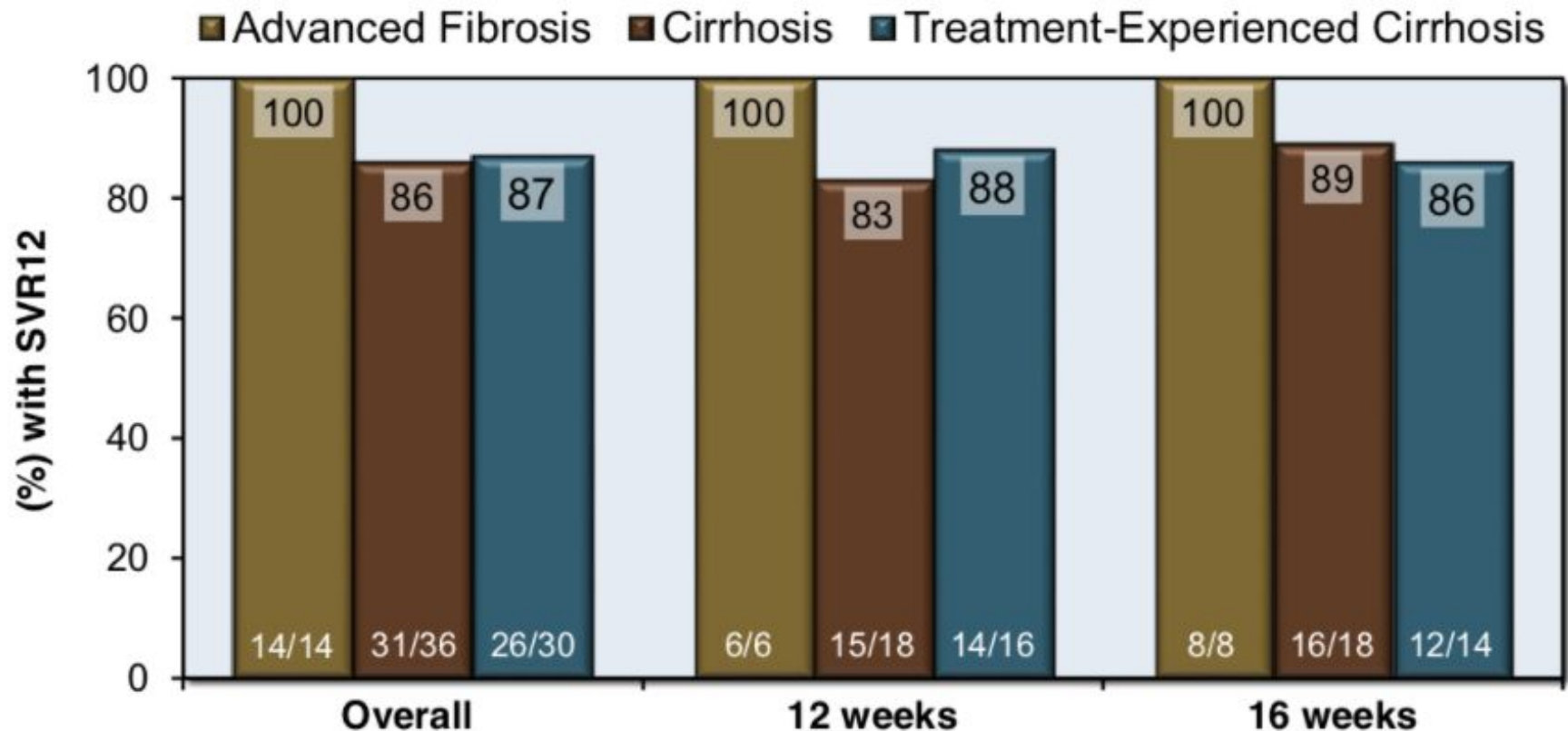
February 28, 2014	July 14, 2014	February 13, 2015
March 31, 2014	July 23, 2014	March 2, 2015
April 4, 2014	July 29, 2014	March 6, 2015
April 10, 2014	August 6, 2014	March 20, 2015
April 28, 2014	August 11, 2014	March 27, 2015
April 29, 2014	August 14, 2014	April 9, 2015
May 2, 2014	August 25, 2014 (X2)	April 24, 2015
May 20, 2014	August 26, 2014	April 30, 2015
June 10, 2014	August 29, 2014	May 8, 2015
June 20, 2014	September 11, 2014	May 22, 2015
June 25, 2014	October 9, 2014	June 9, 2015
June 26, 2014	October 23, 2014	June 19, 2015
June 27, 2014	November 19, 2014	June 24, 2015
June 30, 2014	December 8, 2014	July 10, 2015
July 3, 2014	December 15, 2014	July 16, 2015
July 9, 2014	December 22, 2014	July 21, 2015 (X2)
July 10, 2014	January 9, 2015	July 22, 2015

The February 13, 2015, submission constituted a complete response to our November 25, 2014, action letter.

This new drug application provides for the use of DAKLINZA (daclatasvir) in combination with sofosbuvir for the treatment of chronic hepatitis C virus, genotype 3 infection.

Daclatasvir + Sofosbuvir + RBV for HCV GT 3 Advanced Liver Disease ALLY-3+ Trial: Results

ALLY-3+: SVR12 by Cirrhosis Status



SVR12 rates determined by intent-to-treat analysis

Source: Leroy V, et al. Hepatology 2016 Jan 28. [Epub ahead of print]

NHSE program final data-EASL 2017



The World of Hepatology

THE INTERNATIONAL
LIVER CONGRESS*

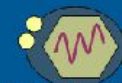
16-20 SEPTEMBER 2017, VIENNA

2017

Real World Outcomes of DAA therapy for chronic hepatitis C virus infection in the HCV Research UK National cohort

W. L. Irving¹, J. McLauchlan², G.R. Foster³, M. Cheung⁴ and HCV Research UK⁴

¹ University of Nottingham, UK; ² University of Glasgow, UK; ³ Queen Mary University of London, UK; ⁴ See Acknowledgements section below



HCV Research UK



INTRODUCTION

Clinical trials of direct-acting antiviral (DAA) therapy for chronic HCV infection have demonstrated very high sustained virological response (SVR) rates.

AIM

To document the performance of DAAs in the UK real-world setting.

METHOD

Patients were recruited from 33 specialist HCV treatment centres participating in the **UK national HCV Research UK cohort**. Any patient with compensated liver disease starting a therapeutic regimen containing a DAA subsequent to 1st July 2015 was eligible for inclusion. Data were entered prospectively on site into a centralised database using a standardised format in Wordpress.

Nationally stipulated DAA regimens were:

- G11 (F0-F4): Abbvie 3D + RBV; SOF/LDV + RBV
- G13 (F3-F4): SOF/PEG/BBV unless IFN intolerant, in which case: SOF/DAC/BBV or SOF/LDV + RBV
- G12 (F4 or Rx experienced): SOF + RBV
- G14 (F0-F4): Abbvie 3D + RBV; SOF/LDV + RBV

RESULTS

This analysis includes data from 1386 patients, 1002 males (72%) and 382 females (28%) [2 unknown]. Age and HCV genotype distributions are shown in figures 1 and 2.

774 patients (56%) were known to have failed previous interferon-based therapy whilst 571 (41%) were treatment naïve

902 patients (65%) were cirrhotic, 484 (35%) were non-cirrhotic

Treatment outcomes:

Overall, **1269 (92%) patients achieved SVR12**; there were 71 virological failures (5%) – 63 responder-relapsers, 7 non-responders and 1 breakthrough; 7 patients died and 39 were lost to follow up

Results for **genotype 1 and 3 patients**, with and without cirrhosis are shown in figures 3-6.

For genotype 2, 13/14 (93%) non-cirrhotic and 29/31 (93%) cirrhotic patients achieved SVR12
For genotype 4, 17/18 (94%) non-cirrhotic and 25/27 (93%) cirrhotic patients achieved SVR12

CONCLUSIONS

- 1) Within this national real-world HCV DAA cohort, SVR12 rates achieved are comparable to those reported from clinical trials.
- 2) With DAA regimens in use in the UK from July 2015 – Feb 2017, genotype 3 infection remains harder to treat than genotype 1, especially in patients with cirrhosis.
- 3) Whilst most patients (91%) were treated with nationally stipulated regimens, nevertheless there was a wide variety (n=19) of different combinations used

Figure 1

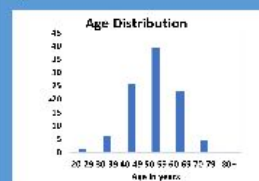


Figure 2

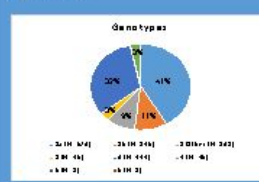


Figure 3

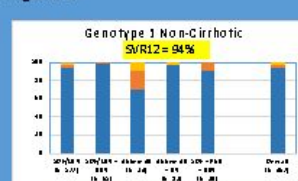


Figure 4

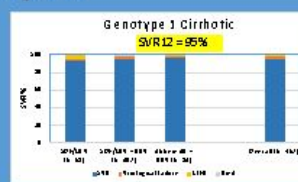


Figure 5

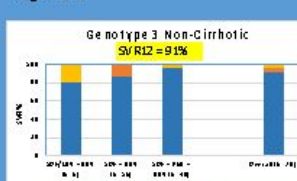
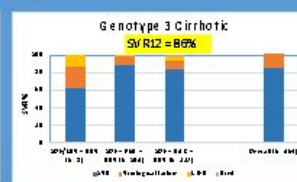


Figure 6



ACKNOWLEDGEMENTS

HCV Research UK Sites and Principal Investigators: Dr. Kish Aggarwal (King's College Hospital, London); Dr. Mark Ainsley (St James' University Hospital, Leeds); Dr. Richard Aspinall (Queen Alexandra Hospital, Portsmouth); Prof. E. Barnes (John Radcliffe Hospital, Oxford); Dr. Stephen Barclay (Glasgow Royal Infirmary); Dr. Chai-Lee Chang (Singapore General Hospital, Singapore); Dr. Lynne Cheung (Hull Royal Infirmary); Dr. Matthew Kemp (Derbyshire Hospital, Plymouth); Prof. John Dillon (Ninewells Hospital, Dundee); Dr. Daniel Forster (St George's Hospital, London); Prof. Graham Foster (Royal London Hospital, Whitechapel, London); Dr. Andrew Fraser (Alder Hey Hospital, Liverpool); Dr. Will Gibson (Addenbrookes Hospital, Cambridge); Dr. W. Gossard (Royal Brompton Hospital); Dr. David Gower (Wycombe General Hospital); Dr. Fiona Gould (Bristol Royal Infirmary); Dr. Brenda Healy (Ulster Hospital, Belfast); Dr. Paul Hines (Portsmouth Hospital); Dr. Adam Lawson (Royal Derby Hospital); Prof. Clifford Leen (Western General Hospital, Edinburgh); Dr. Stuart MacPherson (Freeman Hospital, Newcastle); Dr. Sultana Moazzam (Bridford Royal Infirmary); Prof. David Muller (Queen Elizabeth Hospital, Birmingham); Dr. Matt Priest (Glasgow General Hospital, Glasgow); Dr. Martin Prince (Manchester Royal Infirmary); Dr. Paul Richardson (Royal Liverpool University Hospital); Prof. William Rosenberg (Royal Free Hospital, London); Dr. Stephen Ryder (Queen's Medical Centre, Nottingham); Dr. Ben Stone (Royal Victoria Hospital, Belfast); Prof. Mark Thomas (St Mary's Hospital, London); Dr. Andrew Unwin (North West Leicestershire General Hospital); Dr. S. V. Verma (Royal Sussex County Hospital, Brighton); Prof. Maria Wile (Leicester Royal Infirmary).

The data are due to HCV Research UK staff for establishing the Wordpress database and downloading all the data: Ryan Wilkes, Elizabeth Holtam, Jennifer Benson (all based in Nottingham).

Funding for data collection was kindly provided by Abbvie, Bristol-Myers Squibb and Gilead Sciences

CONTACT INFORMATION FOR HCV RESEARCH UK

Website: www.hcvresearchuk.org
Contact: will.hughes@nottingham.ac.uk or john.mclauchlan@glasgow.ac.uk

DCV-commercial success?

BRISTOL-MYERS SQUIBB COMPANY
WORLDWIDE REVENUES
QUARTERLY REVENUES TREND ANALYSIS
(Unaudited, dollars in millions)

	2016							2017						
	1st Qtr	2nd Qtr	6 Months	3rd Qtr	9 Months	4th Qtr	Year	1st Qtr	2nd Qtr	6 Months	3rd Qtr	9 Months	4th Qtr	Year
Prioritized Brands														
Opdivo	\$ 704	\$ 840	\$ 1,544	\$ 920	\$ 2,464	\$ 1,310	\$ 3,774	\$ 1,127						
Eliquis	734	777	1,511	884	2,395	948	3,343	1,101						
Orencia ^(a)	475	593	1,068	572	1,640	625	2,265	535						
Sprycel	407	451	858	472	1,330	494	1,824	463						
Yervoy	263	241	504	285	789	264	1,053	330						
Empliciti	28	34	62	41	103	47	150	53						
Established Brands														
Hepatitis C Franchise ^(b)	427	546	973	379	1,352	226	1,578	162						
Baraclude	291	299	590	306	896	296	1,192	282						
Sustiva Franchise ^(c)	273	271	544	275	819	246	1,065	184						
Reyataz Franchise	221	247	468	238	706	206	912	193						
Other Brands	568	572	1,140	550	1,690	581	2,271	499						
Total	\$ 4,391	\$ 4,871	\$ 9,262	\$ 4,922	\$ 14,184	\$ 5,243	\$ 19,427	\$ 4,929						

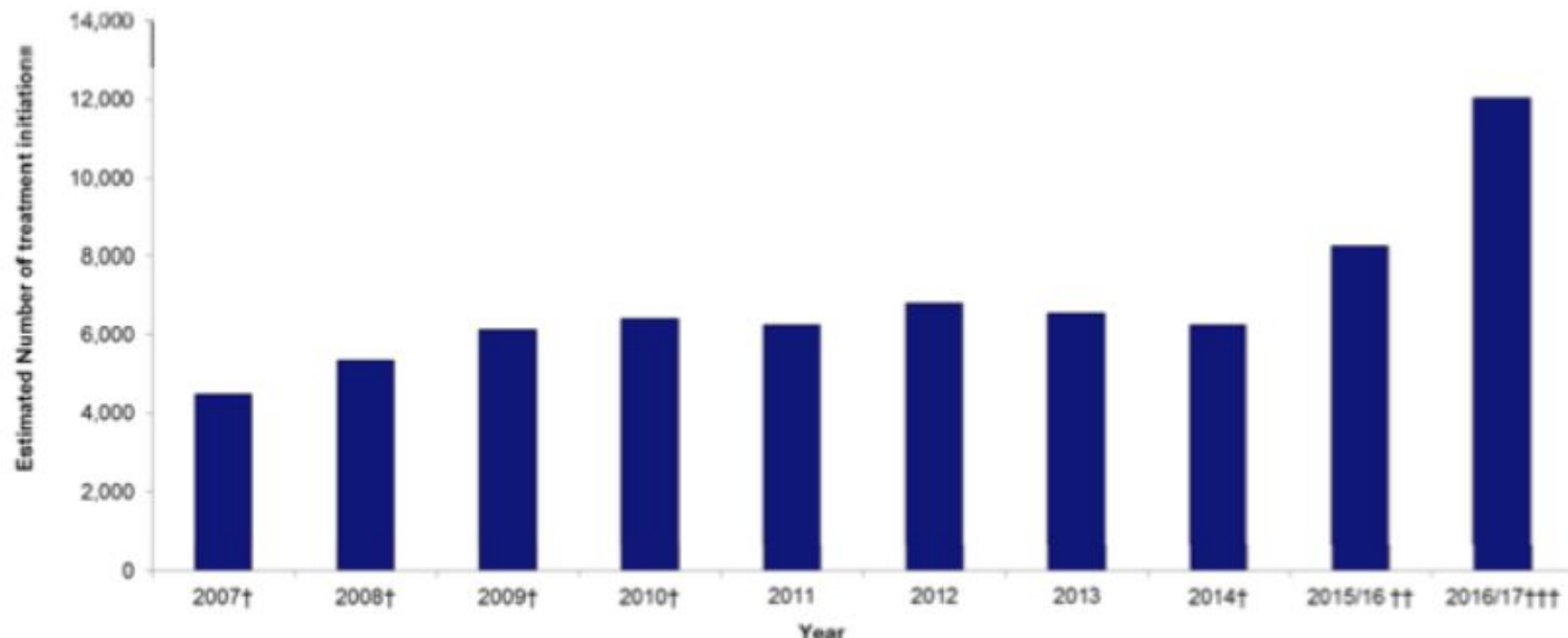
** In excess of +/- 100%

(a) Includes Orencia SubQ revenues of \$244 million and \$216 million for the three months ended March 31, 2017 and 2016, respectively.

(b) Includes Daklinza (daclatasvir) revenues of \$158 million and \$420 million for the three months ended March 31, 2017 and 2016, respectively.

(c) The Sustiva Franchise includes sales of Sustiva and revenue from sales of bulk efavirenz included in the combination therapy, Atripla. Includes alliance revenue of \$158 million and \$241 million respectively.

HCV patients initiating treatment in the UK



* Data for Scotland are only available by financial year between 2007 and 2014 so these have been grouped with calendar years. For example, data for calendar year 2011 are grouped with data for the financial year 2011/12

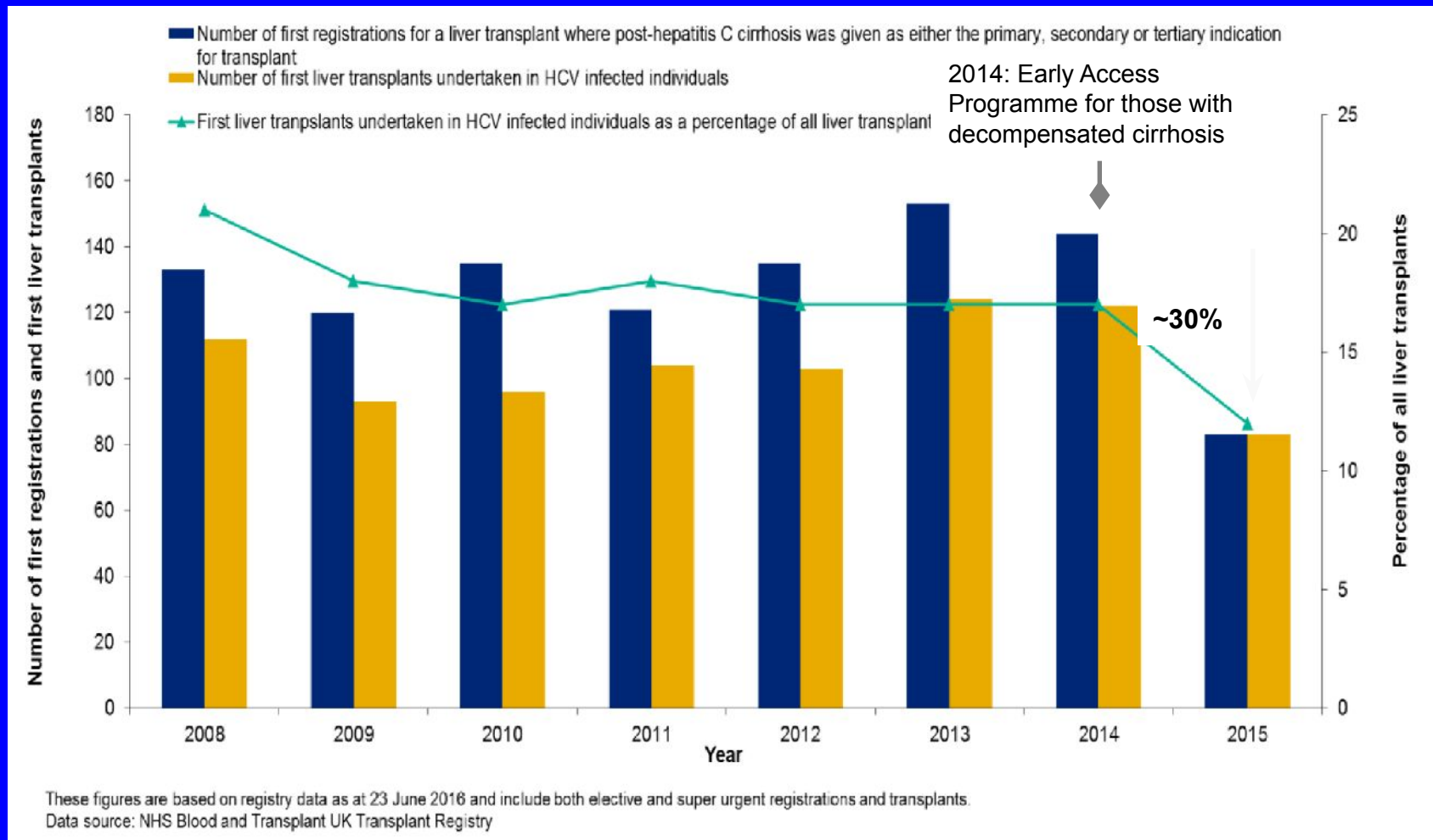
† Data for Wales not available for 2007-2010, and 1 Health Board missing in 2014.

†† Data for 2015/16 are provisional for England and Wales. The method of data collection in Wales changed in 2015, moving to reporting by financial year, and data are revised from the 2016 report; 2015 data for England from the 2016 report have also been revised to allow reporting by financial year from 2015/16, England data are based on new DDA drug treatments only, and on commissioning data which includes clinician intention to treat and invoicing, rather than patient level treatment registry data. These data are subject to data quality issues and contract adjustments.

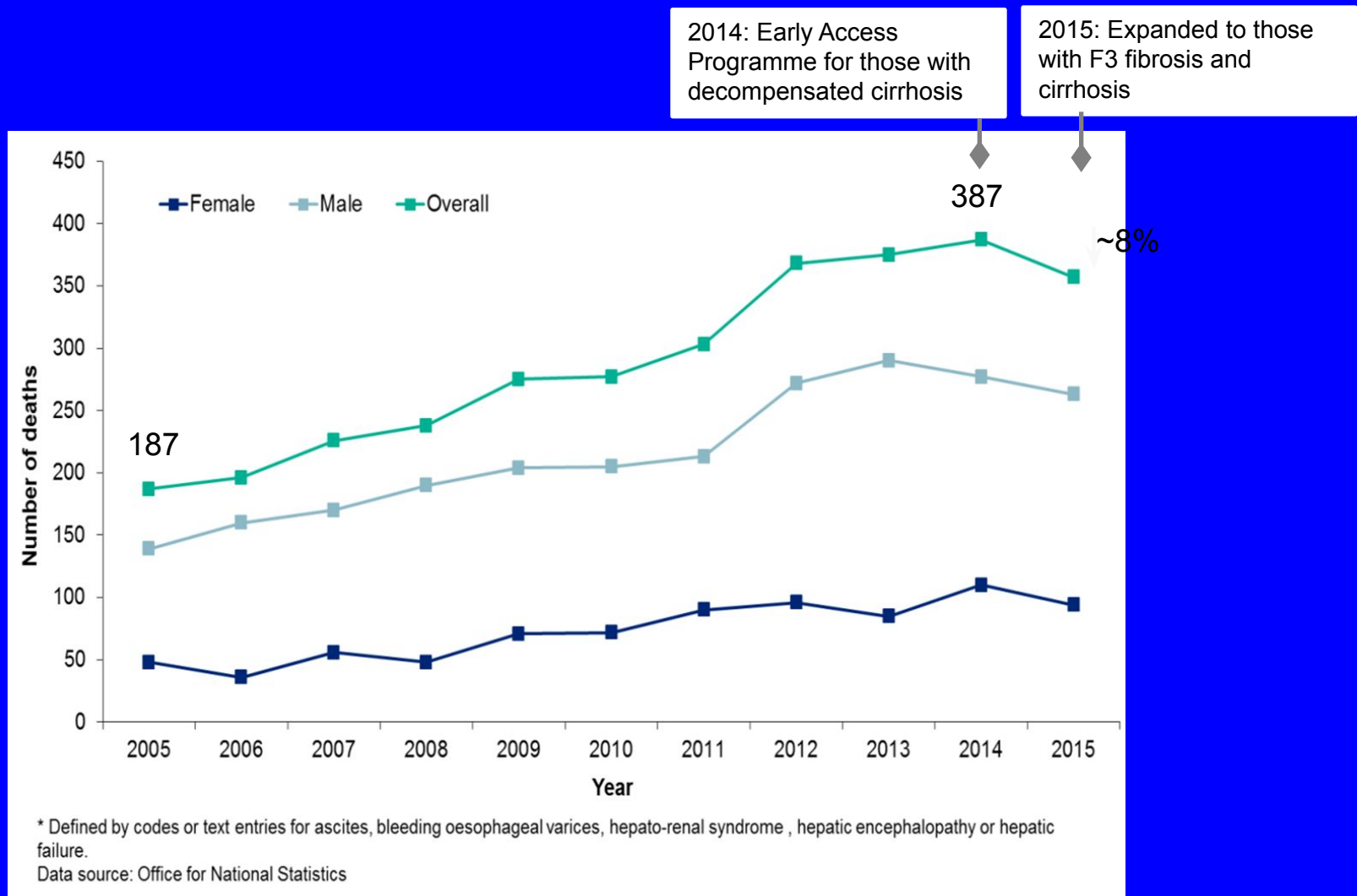
††† Data for 2016/17 are provisional for England, Scotland, and Wales. Data for England are based on new DDA drug treatments only, and on commissioning data which includes clinician intention to treat and invoicing, rather than patient level treatment registry data. These data are subject to data quality issues and contract adjustments.

Data Sources: (i) Regional Hepatology Unit for Northern Ireland; (ii) Health Protection Scotland, using data supplied by hepatitis C treatment centres; (iii) Public Health Wales using data from treatment services in the Health Boards; (iv) NHS England for 2015/2016 and 2016/2017 provisional estimates for England; (v) Sentinel surveillance of hepatitis bloodborne virus testing for scaled estimates for 2012-2014 for England; (vi) Estimates from Roche sales, NHS supply chain manager, and Pharmex data for England for 2007-2011 (Jarvis et al. Journal of Hepatology 2014 vol. 61 | 630-63)

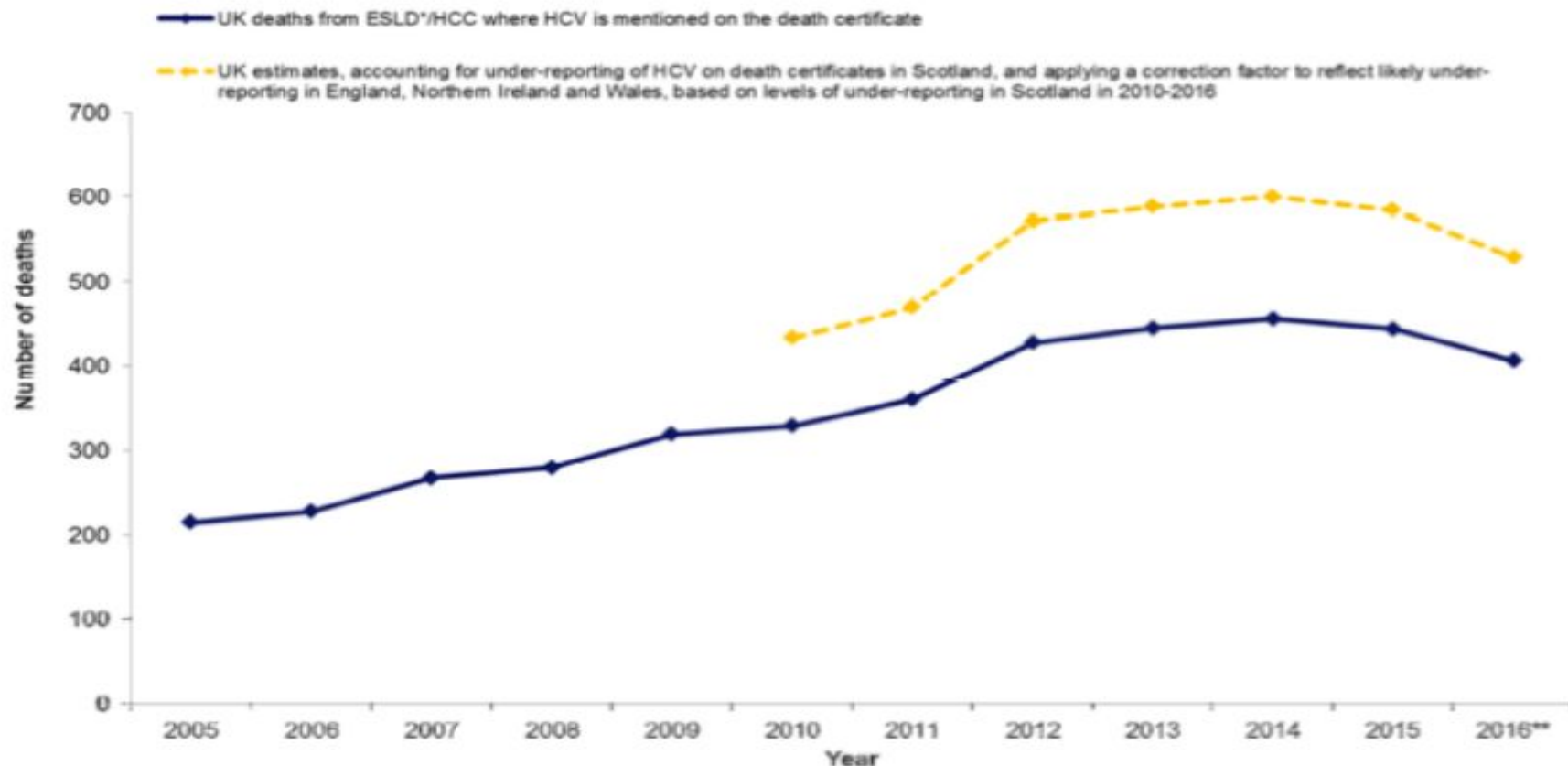
Number of listings and transplants undertaken in England with post HCV cirrhosis i: 2008 - 2015



Deaths from ESLD* or HCC in those with HCV mentioned on their death certificate in England: 2005 to 2015



HCV/HCC deaths in the UK 2007-2016

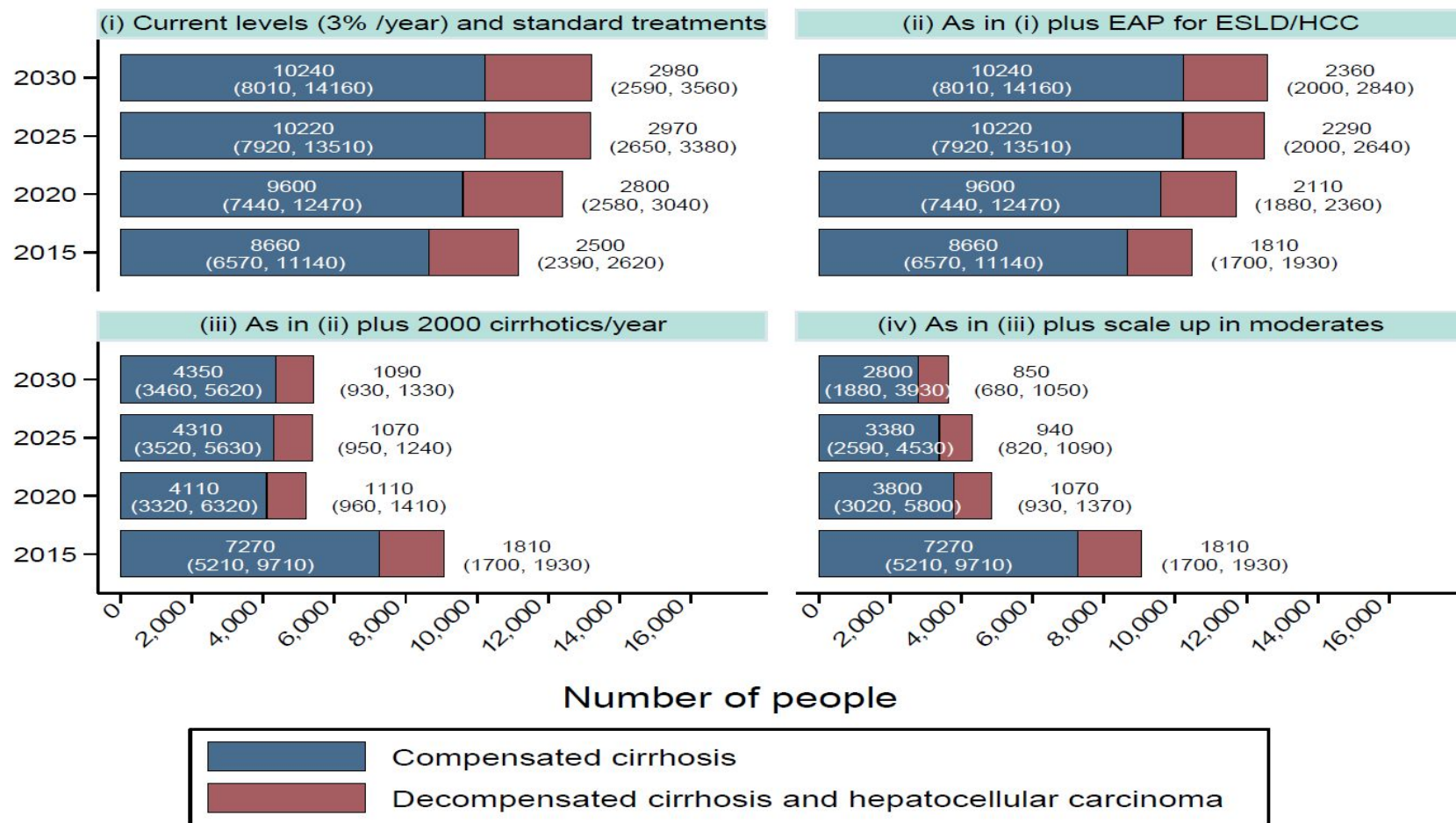


* Defined by codes or text entries for ascites, bleeding oesophageal varices, hepato-renal syndrome, hepatic encephalopathy or hepatic failure.

**2016 data for England and Wales are provisional and based on mortality data as at April 2017, and are missing for Northern Ireland.

Data source: Office for National Statistics for England and Wales; Deaths registration data as supplied by NISRA for Northern Ireland; Health Protection Scotland in association with the Information Services Division

Modelling estimates of number of people living with HCV-related cirrhosis/HCC in England: 2005-2030



Acknowledgements

Aberdeen Royal Infirmary
Addenbrookes Hospital, Cambridge
Birmingham Children's Hospital
Birmingham Heartlands Hospital
Blackpool Victoria Hospital
Bradford Royal Infirmary
Bristol Royal Infirmary
British Liver Trust
Chelsea & Westminster Hospital
Derriford Hospital, Plymouth
Freeman Hospital, Newcastle
Frimley Park Hospital
Gartnavel General Hospital, Glasgow
Glasgow Caledonian University
Glasgow Royal Infirmary
Health Protection Scotland
Hepatitis C Trust
Hull Royal Infirmary
James Cook University Hospital, Middlesbrough
John Radcliffe Hospital, Oxford
Kings College Hospital, London
Leicester Royal Infirmary
Lincoln County Hospital
Manchester Royal Infirmary
Ninewells Hospital, Dundee
North Manchester General Hospital
Public Health England
Queen Alexandra Hospital, Portsmouth
Queen Elizabeth Hospital, Birmingham
Queen's Medical Centre, Nottingham

