Ledipasvir–sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial

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Summary
Background The latest European Association for the Study of the Liver (EASL) guidelines now recommend that patients with acute hepatitis C virus (HCV) infection should be treated with a combination of sofosbuvir and an NS5A inhibitor for 8 weeks. However, the ideal duration of treatment with interferon-free regimens, particularly in HIV-coinfected individuals, remains unknown. We assessed the efficacy and safety of 6 weeks of ledipasvir–sofosbuvir for acute genotype 1 or 4 HCV in HIV-1-coinfected patients.

Methods This open-label, single-arm trial, done in Germany and the UK, included patients with acute HCV genotype 1 or 4 and HIV-1. At screening, patients were either receiving HIV antiretrovirals and had HIV RNA less than 200 copies per mL, or not receiving antiretrovirals and had a CD4 T-cell count of greater than 500 cells per µL. All patients received ledipasvir–sofosbuvir once daily for 6 weeks. The primary efficacy endpoint was the proportion of patients with sustained virological response 12 weeks after the end of treatment (SVR12). This study is registered with ClinicalTrials.gov, number NCT02457611.

Findings Between June 11, 2015, and Jan 8, 2016, we enrolled and treated 26 patients. All (100%) were men, 24 (92%) were white, and 25 (96%) were receiving antiretroviral treatment. 19 (73%) had genotype 1a and seven (27%) had genotype 4 HCV. Overall, 20 (77%; 95% CI 56–91) of 26 patients achieved SVR12: 15 (79%) of 19 with genotype 1a, and five (71%) of seven with genotype 4. Of six patients not achieving SVR12, three relapsed, two achieved sustained virological response 4 weeks after the end of treatment but were lost to follow-up, and one was reinfected. The most common adverse events were fatigue (seven participants [27%]), nasopharyngitis (seven [27%]), and headache (six [23%]). No patient discontinued or interrupted therapy due to adverse events. No HIV rebound occurred during the study.

Interpretation The rate of cure with a fixed-dose combination of ledipasvir–sofosbuvir for patients with acute genotype 1 or 4 HCV infection and HIV-1 coinfection is similar to historic rates with interferon-based treatment, but with shorter treatment duration and more favourable safety outcomes.

Funding Gilead Sciences.

Introduction Interferon-based treatment of acute and early chronic-phase hepatitis C virus (HCV) infection results in higher sustained virological response (SVR) rates than does treatment of chronic HCV infection or treatment of HCV coinfection with human HIV.4 Importantly, SVR12 in acute or early chronic-phase HCV infection was achievable with shortened treatment durations, which has resulted in fewer adverse events and increased the likelihood of optimal adherence. 6 months of interferon alone three times per week achieved HCV cure in 98% of acute HCV monoinfected patients.1 The advent of pegylated interferon given once a week allowed for an even shorter 12-week treatment duration.2 Combination therapy with ribavirin did not increase the SVR rate in patients with acute HCV monoинфекtion, but was considered during treatment for patients with slow response, such as those with HIV coinfection, or in patients with other negative predictors of treatment response.4 With the availability of the better tolerated interferon-free direct-acting antiviral (DAA) drugs, patients presenting with acute HCV are much less willing to undergo interferon-based treatment. This is particularly true for the ongoing outbreak of acute HCV among HIV-seropositive men who have sex with men (MSM). Indeed, uptake of treatment of acute HCV in this population dropped to less than 45% in 2015.3 Because interferon-based therapy takes longer than short courses of DAA combination therapy and is associated with major side-effects, patients often prefer to wait until they reach early chronic infection to receive therapy. The obvious disadvantage of this approach is the potential for onward transmission of HCV to others. Therefore, studies on all-oral DAA-based HCV therapy in patients with acute HCV have been eagerly awaited. Pilot trials have now addressed the efficacy and safety of DAA-based therapy in patients with acute HCV infection. Sofosbuvir and ribavirin combination therapy for shorter treatment durations of 6 weeks led to suboptimal HCV cure rates,
Evidence before this study

We searched PubMed without date restrictions with the terms “acute HCV”, “HIV”, and “DAA” on Sept 30, 2016, and identified 14 entries, six of which were directly applicable to our research background because they studied usage of direct-acting antiviral (DAA) therapy in acute hepatitis C virus (HCV) coinfection with HIV. One was a conference report; the remaining five were reviews, indicating that data and original publications on clinical outcome of interferon-free, DAA-based therapy in acute hepatitis C coinfection with HIV are sparse to date. This sharply contrasts with the wealth of published data and subsequently licensed DAs for treatment of chronic HCV coinfection with HIV. Historically, treatment response rates to interferon-containing therapy were twice as high when therapy was initiated during acute HCV. Data from the NEAT ID funded European PROBE-C cohort showed response rates of about 70% when treating acute HCV in HIV-coinfected patients with interferon with or without ribavirin. However, treatment had to be given at least for 6 months and was associated with clinically significant toxicities. While revolutionising the field of chronic HCV monoinfection and coinfection, implementation of an all-oral DAA-based therapy in the setting of acute HCV is a major unmet medical need. Data from the PROBE-C cohort have shown substantially declining interferon-containing treatment uptake rates, which might further contribute to the ongoing epidemic of acute HCV, particularly among HIV-positive men who have sex with men (MSM).

Added value of this study

Our study has generated data for the efficacy and safety of a short-term fixed-dose combination of two DAs that has already been licensed for treatment of chronic HCV infection (ledipasvir–sofosbuvir), in the treatment of acute HCV in HIV-positive individuals. The overall cure rate of 77% underlines that DAA treatment in the setting of acute HCV coinfection shows similar efficacy to the historic interferon-based treatment. A clear benefit of DAA therapy, however, would be the shorter treatment duration (6 weeks) and the substantially lower rate of laboratory and clinical toxicities. Additionally, our study results for the first time also indicate that the level of HCV viraemia at treatment initiation might have a crucial role in achieving HCV clearance in acute HCV coinfection. Participants with more than 6 million IU/mL HCV RNA at treatment initiation (baseline) were less likely to reach a sustained virological response 12 weeks after the end of treatment (SVR12). Our study also shows the need for behavioural interventions in a high-risk population: one participant was reinfected with HCV shortly after having been cured of his first acute hepatitis C episode.

Implications of all the available evidence

Ideally, our study data will encourage additional all-oral DAA treatment trials in acute HCV to obtain more robust data and to strengthen the new European Association for the Study of the Liver (EASL) guideline recommendations that recommend that patients with acute HCV should be treated with the combination of sofosbuvir and an NS5A inhibitor for 8 weeks, pending additional data establishing the ideal treatment regimen and duration. Several publications modelling the effect of DAs on the acute hepatitis C epidemic among HIV-positive MSM have shown that only wide-scale use of DAs in this high-risk population will help to curtail the epidemic.

Methods

Study design and participants

This open-label, single-arm trial was done at five sites (clinics and hospitals): three in Germany and two in the UK. Patients were enrolled between June 11, 2015, and Sept 3, 2015, and the last patient visit occurred on Jan 8, 2016. Enrolment was open to patients aged at least 18 years who were acutely infected with hepatitis C genotype 1 or 4. Based on the guidelines provided by the European AIDS Treatment Network Acute Hepatitis C Infection Consensus Panel, acute hepatitis C infection was defined as detectable HCV RNA (by PCR assay) with an estimated duration of less than 24 weeks as documented by a first HCV RNA positive and previous negative anti-HCV antibody or HCV RNA test within 6 months of screening, or an increase in liver aminotransferases greater than 2-5 times the upper limit of normal (ULN) within the past 6 months with previous normal aminotransferases in the previous year, provided that other causes of acute hepatitis could be reliably excluded (eg, haemochromatosis, Wilson’s disease, alpha-1 antitrypsin deficiency, or cholangitis). All patients were required to have confirmed infection with HIV-1 and either be receiving an antiretroviral regimen consisting of at least three agents with HIV RNA less than 200 copies per mL and CD4 T-cell count higher than 200 cells per μL at screening, or not be receiving...
antiretroviral treatment and have a CD4 T-cell count higher than 500 cells per μL at screening, to ensure that SVR rates were not affected by more advanced immunodeficiency stages. Patients with active hepatitis B virus infection (positive for HBsAg) were excluded. Patients were also excluded if they had received any treatment for HCV within the previous 6 months. Enrolment of patients with active illicit drug use was allowed, but investigators were allowed to exclude any patient with active alcohol or drug abuse that might present difficulties with protocol compliance.

The study protocol was approved by an institutional review board, and the study was done in accordance with the Declaration of Helsinki and International Conference on Harmonisation guidelines. Written informed consent was obtained from all patients before the initiation of the study.

**Procedures**

All patients received a tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir once daily for 6 weeks. Patients were instructed to take the study drug as near as possible to the same time each day without regard to meals. Study visits occurred at screening, day 1, and at the end of weeks 2, 4, and 6 during treatment. Post-treatment visits occurred at weeks 4 and 12 after the last dose of study drug.

Serum HCV RNA concentrations were assessed with the COBAS AmpliPrep/COBAS TaqMan HCV test (version 2.0) with a lower limit of quantification of 15 IU/mL. HCV genotype was determined using the Siemens VERSANT HCV Genotype INNO-LiPA 2.0 Assay. HIV RNA was measured using the COBAS AmpliPrep/COBAS TaqMan HIV-1 test (version 2.0). Single pharmacokinetic blood samples were collected for all patients at each on-treatment visit. Plasma samples were collected at day 1 and at each visit for viral sequence analysis, as well as at any unscheduled visit initiated for the purpose of confirming virological breakthrough. Deep sequencing of the HCV NSSA and NSSB coding regions was done on samples obtained from all patients at baseline and at virological failure by DDL Diagnostic Laboratory (Rijswijk, Netherlands) using Basic Local Alignment Search Tool (National Center for Biotechnology Information, Bethesda, MD, USA). Resistance-associated substitutions (RASs) that were present in more than 15% of sequence reads are reported.

**Outcomes**

The primary efficacy endpoint of this study was SVR12 (HCV RNA below the lower limit of quantification of 15 IU/mL at 12 weeks after completion of treatment). Secondary efficacy endpoints were the proportion of patients with HCV RNA below the lower limit of quantification during treatment and 4 weeks after completion of treatment (SVR4), the change in HCV RNA from baseline, and the proportion of patients with virological failure. The primary safety endpoint was any adverse event leading to permanent discontinuation of study drug. Safety was assessed in all patients at every visit during and after treatment by physical examination, review of adverse events, and laboratory testing of blood samples.

**Statistical analysis**

No inferential statistics were planned. Efficacy and safety were assessed in the full analysis set, which was defined as all patients who were enrolled in the study and received at least one dose of study drug. The SVR12 rate was calculated along with the two-sided 95% CI using the Clopper-Pearson method for the full analysis set and for prespecified subgroups, including by age (<65 years or ≥65 years), sex, race (black or non-black), baseline body-mass index (BMI; <30 kg/m² or ≥30 kg/m²), baseline alanine aminotransferase (ALT; ≤1·5×ULN or >1·5×ULN), and IFNL3/4 genotype. With about 25 patients with genotype 1 or 4 HCV infection enrolled in the study, a two-sided 95% exact CI of the SVR12 rate was expected to extend to at most 41% in length, calculated by assuming a 50% rate to achieve the maximum binomial variability. Data were analysed with SAS version 9.2.

This study is registered with ClinicalTrials.gov, number NCT02457611.

**Role of the funding source**

The study funder was involved in the design of the study, and the collection, analysis, and interpretation of the data. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

**Results**

34 patients were screened, of whom 26 were enrolled and started treatment. All eight patients who were not enrolled did not meet eligibility criteria (three did not have genotypes 1 or 4 HCV at screening, two did not meet the definition for acute HCV infection, one had HIV RNA greater than 200 copies per mL despite antiretroviral therapy, one had CD4 T-cell count less than 200 cells per μL with antiretroviral treatment, and one was coinfected with hepatitis B virus). Baseline characteristics and demographics of the study population are shown in table 1. At baseline, mean ALT was greatly increased with a median of 95 U/L (range 37–1056) from last available measurements, indicative of acute HCV infection. Only two patients had clinical signs of jaundice, both of whom were on concomitant boosted atazanavir therapy. All patients were men and most were white (table 1). Patients were determined to have acute HCV infection based on study criteria, but the exact duration of acute infection could not be determined for all patients. Most patients had genotype 1a HCV infection (table 1). 25 (96%) of the 26 patients were receiving an antiretroviral regimen at enrolment. The most common HCV
Overall, 20 (77%; 95% CI 56–91) of 26 patients achieved SVR12: 15 (79%; 54–94) of the 19 patients with genotype 1a HCV and five (71%; 29–96) of the seven patients with genotype 4 HCV (table 2). Of the 14 patients with viral load of less than 800 000 IU/mL at baseline, 12 (86%) had SVR12 compared with eight (67%) of 12 of those with viral load 800 000 IU/mL or higher at baseline. By week 2, 19 (73%) of 26 patients had HCV RNA less than the lower limit of quantification. No relation between undetectable HCV RNA at week 2 and SVR12 rates was noted. 11 (92% [95% CI 62–100]) of 12 patients with IFNL3/4 CC genotype of the single nucleotide polymorphism rs12979860 achieved SVR12 compared with nine (64% [35–87]) of 14 with non-CC genotype. None of the other prespecified subgroups had enough patients for an exploratory comparison: no patients were older than 65 years, none were women, only one patient was black, and one had a baseline BMI of 30 kg/m² or higher.

Of the six patients who did not achieve SVR12, three (12%) of 26 experienced virological relapse after the end of treatment and before post-treatment week 4. The main characteristics of the three relapses are summarised in the appendix (p 3). One patient, a 25-year-old white man who had genotype 1a HCV at screening, had undetectable HCV RNA at treatment week 4, did not attend their treatment week 6 visit, and had detectable HCV RNA at post-treatment week 4. Subsequently it was determined that this patient had not relapsed, but was reinfected with genotype 4d HCV infection. Two (8%) of 26 patients were lost to follow-up after completing treatment; both had undetectable HCV RNA at their last visit (post-treatment week 4 for both).

An association was noted between baseline HCV RNA and virological outcome (figure). Of the five patients with HCV RNA greater than 6·96 log₁₀ IU/mL, three relapsed, one achieved SVR12, and one was reinfected. This included all virological failures. Overall, seven patients (one of 17 with genotype 1 HCV infection and all six with genotype 4 HCV infection) had NS5A resistance-associated substitutions (RASs) at baseline. Five (71%) of the seven achieved SVR12, compared with 14 (88%) of the 16 patients without NS5A RASs at baseline. Of the three patients who had virological relapse, one with genotype 1a HCV had NS5A Q30R RAS at baseline and relapse. The patient with genotype 4d HCV had NS5A L30R RAS at both baseline and relapse. The other patient who relapsed had no RASs either before or after treatment. No patient had NS5B RASs at any timepoint.

22 (85%) of the 26 patients had at least one adverse event during the study (table 3). The most common

Table 1: Baseline characteristics

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<thead>
<tr>
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<tr>
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Data are n (%), unless otherwise stated. HCV=hepatitis C virus. LLOQ=lower limit of quantification. SVR4=sustained virological response 4 weeks after the end of treatment. SVR12=sVR 12 weeks after the end of treatment. *One patient had genotype 1a HCV at screening and was reinfected with genotype 4d HCV.

Table 2: Efficacy

See Online for appendix

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An association was noted between baseline HCV RNA and virological outcome (figure). Of the five patients with HCV RNA greater than 6·96 log₁₀ IU/mL at baseline, three relapsed, one achieved SVR12, and one was reinfected. This included all virological failures. Overall, seven patients (one of 17 with genotype 1 HCV infection and all six with genotype 4 HCV infection) had NS5A resistance-associated substitutions (RASs) at baseline. Five (71%) of the seven achieved SVR12, compared with 14 (88%) of the 16 patients without NS5A RASs at baseline. Of the three patients who had virological relapse, one with genotype 1a HCV had NS5A Q30R RAS at baseline and relapse. The patient with genotype 4d HCV had NS5A L30R RAS at both baseline and relapse. The other patient who relapsed had no RASs either before or after treatment. No patient had NS5B RASs at any timepoint.

22 (85%) of the 26 patients had at least one adverse event during the study (table 3). The most common
adverse events were fatigue (seven patients [27%]), nasopharyngitis (seven [27%]), and headache (six [23%]). No patient discontinued or interrupted study treatment due to an adverse event. One patient, a 46-year-old white man with genotype 1a HCV receiving raltegravir plus emtricitabine plus tenofovir disoproxil fumarate, had four serious adverse events—loss of consciousness (on follow-up day 3), serious sequelae of aspiration pneumonia and fever (on follow-up day 5), and thrombophlebitis (on follow-up day 7). All four events had resolved by follow-up day 9.

22 (77%) of 26 patients had at least one laboratory abnormality, most of which were grade 1 (mild) or grade 2 (moderate) in severity. Four (15%) of 26 patients had grade 3 or 4 laboratory abnormalities. A 46-year-old white man with genotype 4 HCV had transient grade 3 increased lipase concentration at week 6 of treatment with normal levels at all other timepoints. This patient also had grade 3 urinary occult blood at post-treatment week 4 and grade 2 urinary occult blood at all other timepoints. Two patients, both of whom were receiving atazanavir plus ritonavir plus emtricitabine plus tenofovir, had asymptomatic increases in bilirubin concentrations.

No patient experienced HIV rebound during the study.

Discussion

Overall, in this single-arm, open-label trial, 20 (77%) of 26 patients with acute HCV genotype 1 or 4 infection and HIV coinfected achieved SVR12 after 6 weeks of HCV therapy with fixed-dose ledipasvir–sofosbuvir. Using the last available HCV RNA results, 22 (85%) of 26 patients were noted to have achieved SVR4 or SVR12, three relapsed within 4 weeks after the end of therapy, and one patient had reinfection with a different genotype between end of treatment and SVR12. This finding clearly underlines that treatment alone of acute or chronic hepatitis C with DAA-based therapy is insufficient but that prevention programmes are also needed to prevent repeated HCV infections. Indeed, management of these patients requires support systems enabling adherence in substance users and high-risk counselling to prevent reinfection. In a recent analysis from the NEAT cohort (cohort of >600 HIV seropositive MSM with cured episode of acute HCV infection) the reinfection rate within the first 2 years after the first acute HCV episode was almost 25%, again emphasising the need for behavioural interventions as well as better education in at-risk groups for HCV transmission.

The three patients who relapsed all had pretreatment HCV viral loads above 6·96 log10 IU/mL suggesting that all-oral DAA-associated HCV elimination might take longer in patients with a high HCV viral burden. This association is well appreciated with treatment of chronic HCV, where shorter treatment durations of 8 weeks have been possible using ledipasvir–sofosbuvir if patients were treatment-naive and had no signs of advanced liver disease. However, treatment durations shorter than 8 weeks, even with the use of three potent DAAs have been associated with high relapse rates in patients with chronic HCV infection.

Overall, 11 (92%) of 12 patients with IFNL3/4 CC genotype achieved SVR12 compared with nine (64%) of 14 patients with non-CC IFNL3/4. Although IFNL3/4 genotype might potentially predict SVR rates, the small number of patients in this study precludes any significant results.
As we have shown here, 6 weeks of DAA-based therapy seems to work for acute HCV in patients with moderate or low viraemia, suggesting that, in the setting of acute HCV, the relatively preserved immune response during acute HCV infection might contribute to HCV clearance. In particular, natural killer cells seem to have an important role in modulating outcome of HCV infection.21

Notably, in the HEPNET study,22 6 weeks of treatment with ledipasvir–sofosbuvir was even more successful in patients with acute HCV without HIV coinfection, with all 20 patients achieving SVR12. However, the number of patients with viral loads higher than $6 \cdot 96 \log_{10}$ IU/mL was smaller in our pilot trial. Interestingly, in the HEPNET study,11 patients with higher baseline HCV RNA levels were more likely to have a week 4 HCV RNA less than 15 IU/mL, but still detectable (vs completely undetectable) than were the patients with lower HCV viral load at baseline, suggesting that baseline viral load could be a key determinant of length of therapy required for sustained viral clearance, even in the setting of acute or early HCV infection. Furthermore, one could speculate that the higher baseline HCV RNA levels in our study population with acute HCV against a background of HIV infection is a result of the HIV-associated perturbation of innate and adaptive immune responses.

Data from other pilot studies of treatment of acute HCV have already shown that sofosbuvir in combination with ribavirin over short treatment durations of 8–12 weeks are associated with high relapse rates, suggesting that the potency of this combination might not be sufficient.19,20 Therefore, in addition to the baseline viral load, potency of the DAA regimen might be another key determinant of length of therapy required for successful clearance in this setting. High SVR rates have also been reported for 4 weeks of ledipasvir–sofosbuvir and 8 weeks of sofosbuvir–simeprevir in acute HCV monoinfection, but precise data for intervals between the diagnosis of acute HCV and start of therapy, as well as median HCV viral load data, are missing.21 This information would be instrumental in better understanding the achieved SVR rates.

In summary, the rate of cure with a fixed-dose combination of ledipasvir–sofosbuvir for patients with acute genotype 1 or 4 HCV infection and HIV-1 coinfection is similar in historic rates with interferon-based treatment, but with shorter treatment duration and more favourable safety outcomes. DAA combination therapy for the treatment of acute HCV seems to be particularly successful even with shorter treatment durations if baseline HCV viral load does not exceed 9 million IU/mL ($6 \cdot 96 \log_{10}$, IU/mL). This could allow for early intervention in a well defined patient group with regular laboratory monitoring because patients come for control of their HIV surrogate markers every 3–6 months, allowing for repeated screening for acute HCV infection, early diagnosis of acute infection, and eventually early intervention, preventing further spread of disease. For patients with acute HCV and HIV coinfection or a baseline HCV RNA level greater than 1 million IU/mL ($6 \cdot 0 \log_{10}$ IU/mL), or both, and an increased risk for relapse the revised EASL guidelines recommend treatment with the same regimens but for 12 weeks. This also accounts for some of the fluctuation that can be expected in HCV levels. Nevertheless, the small number of treated patients and, in particular, low number of included patients with high viral loads limit the generalisability of the data obtained. Further data are needed on shortened DAA therapy in the setting of acute HCV infection (both in people with HCV monoinfection and HCV–HIV coinfection) with larger studies (perhaps randomised) to better understand optimal clinical management of people with acute HCV infection and the potential for shorter treatment options in this population.

The safety data from this pilot trial were encouraging, with few adverse events and no discontinuations due to adverse events. The shorter treatment duration of 6 weeks would further increase the tolerability of this regimen and significantly reduce treatment costs compared with the longer treatment durations for chronic HCV infection.

Contributors

JKR, RHH, CY, and DMB contributed to the study design. JKR, SB, PI, TL, CB, and MN collected the data. WZ and HD-S analysed the data. All authors contributed to the data interpretation, and to the writing and review of the report.

Declaration of interests

JKR has received research grants from Gilead Sciences and ViV, and personal fees from AbbVie, Bionor, Bristol-Myers Squibb, Cipla, Gilead Sciences, Hexal, Janssen, Merck, and Viiv. SB has received personal fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, MSD, and Viiv. RHH, CY, HD-S, WZ, and DMB are employees of Gilead Sciences and hold stock interest in the company. PI has served as a speaker and on advisory boards for Gilead Sciences, AbbVie, and ViV, and has served as a speaker for MSD, Janssen-Cilag, and Bristol-Myers Squibb. TL has received research grants from Bristol-Myers Squibb, AbbVie, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, and MSD, and has received personal fees from AbbVie, Gilead Sciences, ViV, Janssen-Cilag, and MSD. CB has received research grants from NEAT ID, Deutsche Leberstiftung, and DZIF, and has received personal fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, MSD, and ViV. MN has received research grants from Gilead Sciences, has received research grants and personal fees from MSD, Bristol-Myers Squibb, and AbbVie, and has conducted educational research travel and consulted for ViV, GlaxoSmithKline, Boehringer Ingelheim, and Hetero.

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