NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of:

TA96 Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B

TA154 Telbivudine for the treatment of chronic hepatitis B

TA153 Entecavir for the treatment of chronic hepatitis B

TA173 Tenofovir disoproxil fumarate for the treatment of hepatitis B

TA96 – guidance was issued in February 2006. The original review date was February 2007, at which time it was decided to defer the review proposal until the outcomes of TA153 and TA154 were known.

TA154 – guidance was issued in August 2008. The original review date was February 2009.

TA153 – guidance was issued in August 2008. The original review date was February 2009.

In May 2009, there was insufficient new evidence that would materially affect the recommendations in TA96, TA153 and TA154. It was decided to defer the review proposal until March 2012 so that results from ongoing clinical trials comparing combination versus monotherapy for hepatitis B would be available.

TA173 – guidance was issued in July 2009. Review date is March 2012.

1 Recommendation

NICE has been asked to develop a clinical guideline and quality standard on the diagnosis and management of hepatitis B.[1] These projects overlap with the technology appraisals listed above. It is proposed that the technology appraisals are included in the guideline as follows:

- **TA153, TA154, TA173 and recommendation 1.1 of TA96** – These recommendations will be incorporated, verbatim, into the clinical guideline. The technology appraisals will be moved to the static list and will remain extant when the guideline is published. This has the consequence of preserving the funding direction for TA153. TA173 and recommendation 1.1 of TA96. The guideline will contextualise this guidance by considering the place of the

[1] NICE has been given the following remit for the development of a clinical guideline and quality standard.

- To produce a Quality Standard on diagnosis and management of hepatitis B, all ages
- To produce a clinical guideline on the diagnosis and management of hepatitis B in children, adolescents and adults

recommended options within treatment sequences and combination drug regimens.

- **Recommendations 1.2–1.4 of TA96** – These recommendations will be updated by the clinical guideline and will be withdrawn when it is published.

That we consult on these proposals.

2 Original remit(s)

TA96 – To appraise the clinical and cost effectiveness of adefovir dipivoxil and pegylated interferon alfa-2a within their licensed indications for the treatment of chronic hepatitis B virus (HBV) infection.

TA153 – To appraise the clinical and cost effectiveness of entecavir for chronic hepatitis B.

TA154 – To appraise the clinical and cost effectiveness of telbivudine for chronic hepatitis B.

TA173 – To appraise the clinical and cost effectiveness of tenofovir disoproxil fumarate within its licensed indication for the treatment of chronic hepatitis B.

3 Current guidance

TA96

This guidance does not apply to people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or HIV.

1.1 Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications.

1.2 Adefovir dipivoxil is recommended as an option for the treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative) within its licensed indications if:

- treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful, or
- a relapse occurs after successful initial treatment, or
- treatment with interferon alfa or peginterferon alfa-2a is poorly tolerated or contraindicated.

1.3 Adefovir dipivoxil should not normally be given before treatment with lamivudine. It may be used either alone or in combination with lamivudine when:

- treatment with lamivudine has resulted in viral resistance, or

- lamivudine resistance is likely to occur rapidly (for example, in the presence of highly replicative hepatitis B disease), and development of lamivudine resistance is likely to have an adverse outcome (for example, if a flare of the infection is likely to precipitate decompensated liver disease).

1.4 Drug treatment with peginterferon alfa-2a or adefovir dipivoxil should be initiated only by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis. Continuation of therapy under shared-care arrangements with a general practitioner is appropriate.

TA153

This guidance does not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

1.1 Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

TA154

This guidance does not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

1.1 Telbivudine is not recommended for the treatment of chronic hepatitis B.

1.2. People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

TA173

This guidance does not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

1.1 Tenofovir disoproxil, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

4 Rationale[2]

These technology appraisals overlap with the remit of an ongoing clinical guideline and quality standard.

Taken together, the guidance recommends peginterferon alfa an option for the initial treatment of adults with chronic hepatitis B and entecavir or tenofovir disoproxil as options when antiviral treatment is indicated. Telbivudine is not recommended, while adefovir dipivoxil is recommended only in certain circumstances.

[2] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

TA96 was conducted as a multiple technology appraisal (MTA) and the each of the subsequent appraisals was conducted as a single technology appraisal (STA) so the options have never been fully compared with each other and it is not clear at present which of the antiviral drug options should be chosen first, and which should be reserved for second or subsequent line therapy. It is intended that the question of using antiviral drugs within treatment sequences (including those that have been recommended as options by the relevant technology appraisals) will be addressed by the clinical guideline. The guideline will also consider the role of combination regimens of antiviral drugs.

The recommendations of TA153, TA154, TA173 and recommendation 1.1 of TA96 can be incorporated into the guideline while allowing for further guidance to be given on the appropriate use of the recommended options within treatment sequences and combination regimens. However, recommendations in TA96 on adefovir dipivoxil define the place of adefovir dipivoxil in a sequence and have been rendered obsolete by the subsequent technology appraisals, so these recommendations will be updated by the guideline.

This review proposal has been prepared taking into account the principles outlined in the Department of Health policy document PWG IB (10)05. These criteria are outlined in 'Appendix 1 – explanation of options'. The purpose of these criteria is to preserve the funding direction for the recommendations in NICE technology appraisals.

5 Implications for other guidance producing programmes

The Hepatitis B clinical guideline is one of the four pilot topics whereby CCP are developing a guideline in parallel to a quality standard for the first time. The draft scope (consultation from 14th June – 5th July) proposes to cover sequential and combination drug therapy including the four published technology appraisals.

6 New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from 2006 (TA96) 2008 (TA153 and 154) 2009 (TA173) onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7 Summary of evidence and implications for review

Peginterferon alfa-2a and telbivudine have marketing authorisations for the treatment of chronic hepatitis B in adult patients with compensated liver disease. The marketing authorisations have not changed since publication of their respective guidance (TA96 and TA154).

The marketing authorisation for adefovir dipivoxil is also unchanged since the publication of TA96, and allows the treatment to be given to patients with either *compensated* or *decompensated* liver disease.

Tenofovir disoproxil and entecavir had marketing authorisations for "*the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis*" at the time of publication of TA173 and 153, respectively. However, both of these treatments have been granted extensions to their licences (in July 2010 and March 2011) to also include treatment of chronic hepatitis B in adults with "*decompensated liver disease*".

Decompensated liver disease is characterised by failure of the liver to maintain adequate function and represents the end stage of liver disease. If untreated, the survival of patients with decompensated liver cirrhosis is poor (~15% at 5 years).

Following the extensions to the marketing authorisations, a draft scope was sent out for consultation in September 2010 which proposed a MTA of entecavir and tenofovir disoproxil fumarate for the treatment of chronic hepatitis B in adults with decompensated liver disease. Responses from consultees and commentators indicated that the size of the population with decompensated liver disease is small and difficult to estimate. NICE contacted several experts in the area of hepatitis B who were unable to confirm the estimated proportion of patients in the UK with decompensated liver disease in the absence of robust data. It was also noted that the BNF (version 60) stated that entecavir alone, tenofovir disoproxil alone, or a combination of lamivudine with adefovir dipivoxil can be used in patients with decompensated liver disease, even though entecavir and tenofovir disoproxil were not licensed for decompensated disease at that time. It was noted that a clinical guideline (Diagnosis and management of hepatitis B in children, adolescents and adults) had also recently been referred to NICE, and therefore a decision was made to wait to finalise the scope for the proposed MTA until the scope of the clinical guideline was finalised (in August 2011).

With regard to the availability of new evidence relating to the indications considered in technology appraisal guidance 96, 153, 154 and 173, a large number of studies were identified since their publication. Approximately 126, 57, 17 and 15 references were identified relating to TA96, TA153, TA154 and TA173, respectively.

Of the 126 references identified for TA96, many were either not directly relevant or small studies. Only nine phase III randomised controlled trials were found that were directly relevant to the current guidance. These largely support the recommendations in the current technology appraisal. Of note, many studies (which were also identified in the TA173 searches) featured comparisons of adefovir dipivoxil with tenofovir disoproxil, and demonstrated the superior efficacy of tenofovir disoproxil. Two studies concluded that peginterferon alfa-2a was superior to entecavir in achieving HBeAg sero-conversion and in reducing HBeAg and HBsAg levels in patients with HBeAg-positive chronic hepatitis (Chen et al, 2009 (1); Chen et al, 2009 (2)).

There were 57 references identified relating to entecavir (TA153). Of these, 24 were relevant randomised studies although few were large phase III trials. Many of the studies assessed the efficacy of entecavir compared with lamivudine or adefovir dipivoxil. There were some contrasting conclusions from the authors on the rate of entecavir-resistance over 3- and 5-year study periods (Suzuki et al, 2009; Tenney et al, 2009).Several studies suggested that entecavir is superior to adefovir dipivoxil in suppressing hepatitis B virus replication.

Several publications were identified relating to the use of tenofovir disoproxil in patients with decompensated liver disease. One of the studies concluded that tenofovir disoproxil reduces HBV-DNA levels, MELD (model for end-stage liver disease) scores, and reduces mortality in patients with spontaneous reactivation of CHB presenting as acute-on-chronic liver failure. A meta-analysis looking at the use of long-term nucleos(t)ide analogues in patients with chronic hepatitis B concluded that these agents prevent or delay long-term complications including decompensated cirrhosis (liver disease).

A phase II study compared tenofovir disoproxil and entecavir in patients with decompensated chronic hepatitis B liver disease. Both treatments were well tolerated in these patients (Liaw et al 2011).

Although a large number of studies have been published since TA96, TA153, TA154 and TA173 were issued, about the five technologies in these guidance documents, the majority of the data supports the current recommendations. Although two technologies have achieved extensions to their marketing authorisations to include decompensated liver disease, it may be more appropriate to consider the implications of these licence extensions in the context of an MTA (a scope has already been consulted on), or as part of the ongoing Clinical Guideline on hepatitis B. Either of these approaches may be more suitable considering that patients with decompensated disease are at different stage of disease with a much worse prognosis than those with compensated disease, which the current guidance currently focuses on. In light of this, it is recommended that a review of TA96, TA153, TA154 and TA173 is deferred and the guidance is placed on the static guidance list until new evidence becomes available which is likely to materially effect the current recommendations. It is proposed that the current recommendations in these guidance documents are incorporated into the ongoing clinical guideline for the management of hepatitis B. It is also proposed that the licence extensions for entecavir and tenofovir for decompensated liver disease are considered as either a separate technology appraisal or as part of the ongoing clinical guideline (if appropriate following the scoping process for the clinical guideline).

8 Implementation

Based on the implementation advice received, there was an increase in prescribing costs for entecavir in both primary and secondary care following the publication of NICE technology appraisals 153 and 154 and curtailed slightly (in secondary care) following the publication of TA 173.

The prescribing of telbivudine initially increased following publication of TA 153 an 154, however, upon the publication of TA 173 prescribing has gradually fallen. Importantly, the relative prescribing volume and costs of telbivudine is considerably smaller than entecavir, tenofovir disoproxil, adefovir dipivoxil and peginterferon alfa-2a, suggesting that NICE guidance is being adhered to.

Tenofovir disoproxil prescribing has shown a fall from 2005 only to plateau around the time of the publication of TA153 and 154. It is important to note that tenofovir disoproxil is also licensed for the treatment of HIV-1 infection and this fall is likely to reflect the reduction in prescribing for HIV-1. In addition, tenofovir disoproxil only received its marketing authorisation for chronic hepatitis B in March 2008. Since the

publication of TA173, there has been a relatively small increase in tenofovir disoproxil prescribing. However, the prescribing data might hide any increase in the use of tenofivir disoproxil for chronic hepatitis B if the number of prescriptions for HIV-1 continued to fall.

Prescribing costs for both peginterferon alfa-2a and adefovir dipivoxil increased following the publication of TA96 (2006). However, upon the publication of Appraisal Consultation Document (ACD) for TA153 in April 2008, adefovir dipivoxil prescribing costs began to fall, (perhaps as a result of increased uptake of entecavir) and this trend has continued. The prescribing costs for peginterferon alfa-2a have continued to rise since the publication of TA96, and despite showing a fall between April 2008 and March 2009 (publication of TA153 ACD). Again, it is worth noting that peginterferon alfa-2a is also licensed for the treatment of Hepatitis C.

In summary, the sequential publication of technology appraisals 96, 153, 154 and 173 appear to have had an impact on prescribing practices and these practices seem to largely adhere to NICE guidance.

9 Equality issues

No equalities issues were highlighted during the appraisals for TA96, TA153, TA154 or TA173. No equalities issues were raised during the scoping process for the proposed MTA of entecavir and tenofovir for decompensated liver disease.

GE paper sign off: Janet Robertson, 14th July 2011

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	If the on-going guideline incorporates the technology appraisal guidance, it will include the recommendations of the technology appraisal verbatim. The technology appraisal will remain extant alongside the guideline and it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	TA153, TA154, TA173 and recommendation 1.1 of TA96 will be incorporated into the guideline. The technology appraisals will be moved to the static list and will remain extant when the guideline is published This has the consequence of preserving the funding direction for TA153. TA173 and recommendation 1.1 of TA96.

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	Recommendations 1.2–1.4 of TA96 have been rendered obsolete by subsequent recommendations and will be updated by the clinical guideline. These recommendations will be withdrawn when the guideline is published.
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	This would be a consequence of incorporating into the guideline (see above).

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

In progress

Public Health Guidance: Hepatitis B and C: ways to promote and offer testing to people at risk of infection. Expected date of issue: Dec 2012

Clinical Guideline: The diagnosis and management of hepatitis B in children, adolescents and adults. Expected date of issue: to be confirmed.

Suspended/terminated

Entecavir and tenofovir disoproxil fumarate for the treatment of chronic hepatitis B in adults with decompensated liver disease. Suspended until the outcome of the scoping process for the Clinical Guideline (The diagnosis and management of hepatitis B in children, adolescents and adults) is known.

In topic selection[3]

[redacted]

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Tenofovir disoproxil has a marketing authorisation in the UK for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.	In addition to these indications listed, the SPC says tenofovir disoproxil also is indicated for: • decompensated liver disease

[3] Information held by the NICE Topic Selection Team is treated as being potentially commercially sensitive by default. Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

Indication considered in original appraisal	Proposed indication (for this appraisal)
Entacavir has a marketing authorisation in the UK for the treatment of chronic HBV infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.	In addition to these indications listed, the SPC says tenofovir disoproxil also is indicated for: • decompensated liver disease

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
None identified	

Registered and unpublished trials

Trial name and registration number	Details
A comparative study of chronic hepatitis B subjects treated with entecavir plus tenofovir combination therapy vs. entecavir monotherapy in adults who are treatment-naive to nucleosides and nucleotides: The BE-LOW study. (NCT00410072)	Phase III study. Estimated completion date: March 2011. Status: ongoing but not recruiting. (This trial is alluded to in the research recommendations, which say: "6.1 A phase III trial of entecavir plus tenofovir disoproxil combination therapy versus entecavir monotherapy in treatment-naive people with chronic hepatitis B is currently recruiting participants.")
A randomized, double-blind, controlled evaluation of tenofovir df versus adefovir dipivoxil for the treatment of HBeAg positive chronic Hepatitis B (NCT00116805)	Phase III study. Estimated completion date: June 2014. Status: ongoing but not recruiting.

Trial name and registration number	Details
A randomized, double-blind, controlled evaluation of Tenofovir DF versus Adefovir Dipivoxil for the treatment of presumed pre-core mutant chronic Hepatitis B (NCT00117676)	Phase III study. Estimated completion date: May 2014. Status: ongoing but not recruiting. (This trial appears to relate to one of the research recommendations, which says: "6.2 Research on the long-term risk of resistance with tenofovir disoproxil monotherapy and tenofovir disoproxil in combination with other antiviral agents is needed because few RCTs are currently available.
A study of the safety and efficacy of Entecavir plus Tenofovir in adults with chronic Hepatitis B virus infection with previous nucleoside/nucleotide treatment failure (NCT01063036)	Phase III study. Estimated completion date: October 2013. Status: currently recruiting.
A multi-centre, double blind, double dummy, randomised, controlled study to evaluate the efficacy and safety of TDF 300mg once daily (QD) versus Adefovir Dipivoxil (ADV) 10mg QD in Chinese subjects with CHB (NCT01300234)	Phase III study. Estimated completion date: December 2016. Status: not yet open for recruitment.
A randomized, open-label, controlled, exploratory trial to characterize the results of daily oral administration of Telbivudine 600 mg and Tenofovir Disproxil Fumarate 300 mg in combination or Telbivudine 600 mg or Tenofovir Disproxil Fumarate 300 mg monotherapy given over 12 weeks on the kinetics of Hepatitis B virus DNA in adults with HBeAg positive compensated CHB (NCT00805675)	Phase III study. Estimated completion date: September 2010. Status: currently recruiting.

Trial name and registration number	Details
Study to Evaluate the Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) in Combination With Peginterferon α-2a vs Standard of Care Tenofovir Disoproxil Fumarate Monotherapy or Peginterferon α-2a Monotherapy for 48 Weeks in Chronic Hepatitis B(CHB). (TDF PEG CHB) (NCT01277601)	Phase IV study. Study Start Date: March 2011. Estimated Study Completion Date: October 2014

Trial name and registration number	Details
Augmenting Response to Entecavir With Peginterferon a-2a for the Treatment of HBeAg-positive Chronic Hepatitis B (ARES) (NCT00877760)	Study Start Date: August 2009. Estimated Study Completion Date: September 2013
A Study of Combination or Sequential Treatment With PEGASYS (Peginterferon Alfa-2a (40KD))and Entecavir in Patients With HBeAg Positive Chronic Hepatitis B (NCT00940485)	Phase IV study. Study Start Date: June 2009. Estimated Study Completion Date: December 2011
Optimal Combination Therapy for Multi-drug Refractory Chronic Hepatitis B Patients (CAESAR-L) (NCT01023217)	Phase IV study. Study Start Date: November 2009. Estimated Study Completion Date: October 2012
Lamivudine Plus Adefovir Versus Telbivudine Plus Adefovir in Lamivudine Resistant Chronic Hepatitis B (NCT01270165)	Phase III. Study Start Date: June 2010. Estimated Study Completion Date: May 2012
A Study of PEGASYS (Peginterferon Alfa-2a (40KD)) in Combination With Adefovir or Entecavir in Patients With HBeAg-Positive Chronic Hepatitis B (NCT00922207)	Phase IV. Study Start Date: August 2008. Estimated Study Completion Date: December 2012
Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) 300mg in Chinese Subjects With Chronic Hepatitis B (CHB) (TDF in CHB) (NCT01300234)	Phase III. Study Start Date: March 2011. Estimated Study Completion Date: December 2016
Entecavir Plus Adefovir Combination Therapy Versus Entecavir Monotherapy vs Therapy With Adefovir Plus Lamivudine for Chronic Hepatitis B Infected Subjects With Lamivudine-resistant Virus (DEFINE) (NCT00410202)	Phase III. Study Start Date: March 2008. Estimated Study Completion Date: June 2012
Efficacy and Safety Study of Entecavir Plus Tenofovir in Patients With Chronic Hepatitis B Who Failed Previous Treatment (NCT01063036)	Phase III. Study Start Date: May 2010. Estimated Study Completion Date: October 2013
Lamivudine Plus Adefovir Versus Telbivudine Plus Adefovir in Lamivudine Resistant Chronic Hepatitis B (NCT01270165)	Phase III. Study Start Date: June 2010. Estimated Study Completion Date: May 2012

Trial name and registration number	Details
Telbivudine Versus Lamivudine for Maintenance Therapy of Patients With Chronic Hepatitis B and Negative HBV Viral Load After 6 Month of Treatment With Telbivudine (SASL28) (NCT01005238)	Phase IV. Study Start Date: September 2009. Estimated Primary Completion Date: December 2014
Efficacy of Telbivudine Treatment at Long Term on the Absence of Liver Inflammation in Patients With Compensated Chronic Hepatitis B (NCT00877149)	Phase IV. Study Start Date: March 2009. Estimated Primary Completion Date: July 2011
Efficacy of Telbivudine in Blacks/African Americans and Hispanics/Latinos With Compensated Chronic Hepatitis B During 52 Weeks (NCT00862706)	Phase IV. Study Start Date: April 2009. Estimated Primary Completion Date: August 2011
EFFicacy Optimization Research of Telbivudine Therapy (EFFORT) (NCT00962533)	Phase IV. Study Start Date: August 2009. Estimated Study Completion Date: August 2012
ADVANCE Study: A Study of PEGASYS (Peginterferon Alfa-2a (40KD)) + Adefovir Dipivoxil in Patients With Hbe(-) Chronic Hepatitis B (NCT00661076)	Phase IV. Study Start Date: August 2008. Estimated Study Completion Date: March 2012
A Single-arm Study Evaluating the Efficacy and Safety of Telbivudine With or Without add-on Tenofovir in Adults With HBeAg-positive Chronic Hepatitis B (CHB) (NCT00651209)	Phase IV. Study Start Date: February 2008. Estimated Study Completion Date: July 2011
Study to Evaluate the Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) in Combination With Peginterferon α-2a vs Standard of Care Tenofovir Disoproxil Fumarate Monotherapy or Peginterferon α-2a Monotherapy for 48 Weeks in Chronic Hepatitis B(CHB). (TDF PEG CHB) (NCT01277601)	Phase IV. Study Start Date: March 2011. Estimated Study Completion Date: October 2014

Trial name and registration number	Details
A Phase 3b, Randomized, Double-Blind, Double-Dummy Study Evaluating the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate (DF) Monotherapy Versus Emtricitabine Plus Tenofovir DF Fixed-Dose Combination Therapy in Subjects With Chronic Hepatitis B Who Are Resistant to Lamivudine (NCT00737568)	Phase IV. Study Start Date: October 2008. Estimated Study Completion Date: August 2014
FINITE CHB - First Investigation in Stopping Tenofovir Disoproxil Fumarate (TDF) Treatment After Long Term Virologic Suppression in HBeAg-negative Chronic Hepatitis B (NCT01320943)	Phase IV. Study Start Date: March 2011. Estimated Study Completion Date: December 2014

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