15 October 2020
EMA/578690/2020
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Pegasys

peginterferon alfa-2a

Procedure no: EMEA/H/C/000395/P46/057

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 13th July 2020, the MAH submitted a completed paediatric study for Pegasys® (pegylated-interferon alfa-2a), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study NV25361: *Phase IIIb, Randomized, Open-Label Study of Pegylated Interferon Alfa-2a in Combination with Lamivudine or Entecavir Compared with Untreated Control Patients in Children with HBeAg-Positive Chronic Hepatitis B in the Immune-Tolerant Phase* is a stand-alone study.

The NEPTUNE study (Study WV19432) was a non-inferiority Phase IV trial that confirmed the efficacy of a regimen of Pegasys® 180µg/week for 48 weeks in adults with HBeAg-positive chronic HBV infection. This does was modified for paediatric use in order to achieve similar exposures to the authorised adult dose (Schwarz et al. 2006).

Subsequently, Study NV25361 aimed to evaluate the efficacy and safety of treating children with immune-tolerant CHB disease, with therapy duration based on those used in two pilot studies where this particular treatment strategy was first tested (D'Antiga et al. 2006; Poddar et al. 2013). This study was originally specified as a clinical measure in the Paediatric Investigation Plan agreed for Pegasys® but was removed as a result of modification procedure EMEA-000298-PIP01-08-M06 (decision P/0143/2018).

2.2. Information on the pharmaceutical formulation used in the study

In study NV25361, Pegasys® 180 µg/mL (1 mL solution in 2-mL vials) was administered subcutaneously once weekly. This formulation and strength is already authorised for the treatment of HBeAg-positive CHB in non-cirrhotic children and adolescents 3 years of age and older with evidence of viral replication and persistently elevated serum ALT levels.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final abbreviated clinical study report (CSR) for a prematurely terminated paediatric clinical study:

- Study NV25361: *Phase IIIb, Randomized, Open-Label Study of Pegylated Interferon Alfa-2a in Combination with Lamivudine or Entecavir Compared with Untreated Control Patients in Children with HBeAg-Positive Chronic Hepatitis B in the Immune-Tolerant Phase*

2.3.2. Clinical study

Study NV25361

Phase IIIb, Randomized, Open-Label Study of Pegylated Interferon Alfa-2a in Combination with Lamivudine or Entecavir Compared with Untreated Control Patients in Children with HBeAg-Positive Chronic Hepatitis B in the Immune-Tolerant Phase

Description

Methods

Objectives

The original study objectives specified in the study protocol were:

Efficacy

- Primary efficacy: of Pegasys® + lamivudine or entecavir for 48 weeks compared with an untreated control in children with CHB, as measured by loss of HBsAg 24 weeks post treatment/ end of untreated observation.
- Secondary efficacy: of Pegasys® + lamivudine or entecavir compared with an untreated control in children with CHB, as measured by seroconversion to anti-HBs, seroconversion to anti-HBe, loss of HBeAg, and HBV DNA levels, at 24 weeks post-treatment/end of untreated observation

  And

  Pegasys® + lamivudine or entecavir in children with CHB, as measured by seroconversion to anti-HBs, seroconversion to anti-HBe, loss of HBsAg, loss of HBeAg, HBV DNA levels, at 1 yearpost-treatment.

Safety

- of the Pegasys® + lamivudine or entecavir group compared with the untreated control group in children with CHB, by assessment of adverse events (including neuropsychiatric assessment), laboratory test results (including thyroid function), vital signs and growth, up to 24 weeks post-treatment/end of untreated observation and up to 1 year post-treatment.

Pharmacokinetic

- of Pegasys® in children with CHB treated with Pegasys® + lamivudine or entecavir following administration of a body surface area (BSA)–based dosing regimen.

Exploratory

- Relationship between quantitative HBsAg/quantitative HBeAg and treatment response in children with CHB.
- Lamivudine or entecavir viral resistance in children with CHB.
- Incidence of anti-drug antibodies (ADAs) in children with CHB treated with Pegasys® + lamivudine or entecavir.

Assessment comment:

This Phase 3 study was designed to evaluate the efficacy of Pegasys® in combination with lamivudine or entecavir in paediatric patients with chronic, immune-tolerant hepatitis B, who historically have not been actively treated, on the basis that seroconversion rates were too low to justify the clinical burden and risks of treatment. The rationale for this was promising results from two small pilot studies treating pediatric patients with CHB in the immune-tolerant phase reported results for the treatment groups showing more frequent HBeAg and HBsAg loss, seroconversion, and sustained virological responses, as compared with untreated controls (D'Antiga et al. 2006; Poddar et al. 2013).

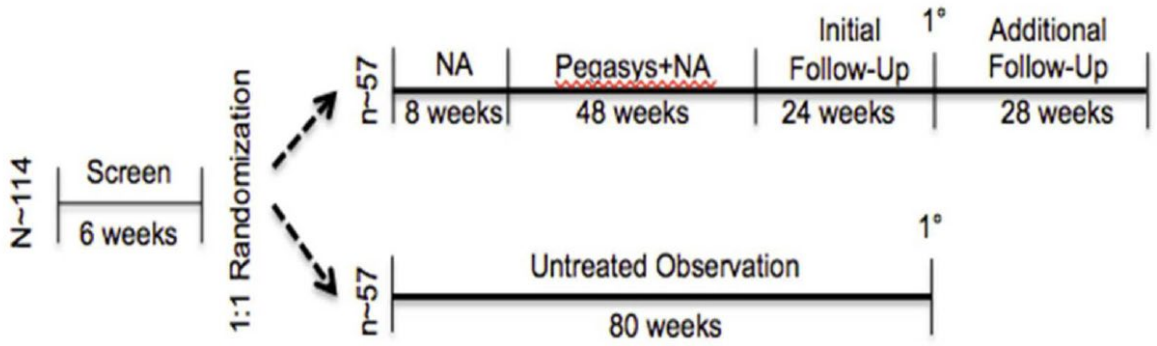
Study design

The study began as a single-site investigator-sponsored trial (King's College Hospital/King's College London) with three arms (Pegasys® monotherapy, Pegasys®+lamivudine, and untreated control), from which 3 patients in the Pegasys® monotherapy arm (Group C), 2 patients in the Pegasys® + lamivudine and 6 patients in the untreated arm who signed an updated Informed Consent/Data Release form are included in the CSR. Patients who did not sign an updated Informed Consent/Data Release form (n=10) were not included in the CSR as their data were not released to Roche.

The study was subsequently transferred to Roche and changed to an open-label, randomised, controlled, parallel group, multi-centre superiority study in 114 children, aged 3 to less than 18 years with immune-tolerant CHB, stratified by HBV genotype A vs. B/C vs. D/other) and randomized 1:1 to either lamivudine or entecavir alone for 8 weeks followed by Pegasys® + lamivudine or entecavir for 48 weeks (Group A) or no treatment (Group B). The Pegasys® monotherapy arm was removed following concerns regarding the probable low response rates to treatment with Pegasys® monotherapy raised by the study Data Safety Monitoring Board (DSMB) members and potential study investigators during feasibility assessment.

For treated patients, the approximate intended study length was 2 years and 2 months (up to 6 weeks' screening, 8 weeks' lamivudine or entecavir treatment, 48 weeks' Pegasys® + lamivudine or entecavir treatment, 24 weeks' initial follow-up, 28 weeks' additional follow-up). For untreated patients, the intended approximate study length was 1.5 years (up to 6 weeks' screening and 80 weeks' untreated observation).

Figure 1. Schematic of design of Study NV25361



NA =nucleoside analog (lamivudine or entecavir).

Source: CSR Study NV25361 Figure 1.

Assessment comment:

The use of an untreated control group was adequately justified on the basis of lack of existing established treatment for the target population, difficulty in blinding due to the well-known side effect profile of Pegasys®, and lack of ethical justification for administering weekly placebo injections for 48 weeks. This is not considered problematic for analysis of the efficacy endpoints, which are objective laboratory assays of virological markers of disease.

The results from two multicentre clinical trials with a similar design to Study NV25361, sponsored by the National Institutes of Health (NIH), evaluating the entecavir + Pegasys® treatment regimen in

patients with immune-tolerant chronic hepatitis B (CHB) were made available in October 2017 at the American Association for the Study of Liver Diseases Congress in Washington, USA (Rosenthal et al. 2017 [paediatric patients]; Feld et al. 2017 [adult patients]). Both studies demonstrated minimal to no efficacy of the intervention in adult and paediatric patient populations with immune-tolerant CHB. The combination of entecavir + Pegasys®, administered for up to 48 weeks, rarely led to loss of hepatitis B envelope antigen with sustained suppression of hepatitis B virus (HBV) DNA levels and was associated with frequent but not serious adverse events. Based on these results the PDCO agreed in March 2018 to modify the PIP for Pegasys® and remove Study NV25361 from the PIP commitments. The study was also removed from the Risk Management Plan (RMP). Following this, Roche terminated recruitment to the study on 28 March 2018 in accordance with the recommendation from the Data Safety Monitoring Board (DSMB) on 22 March 2018, which considered that the NIH results demonstrating minimal efficacy changed the benefit- risk balance of Pegasys® + lamivudine or entecavir in immune-tolerant CHB. No specific safety concerns were identified in their scheduled review of the study.

Study population

Children 3 to <18 years of age with immune-tolerant CHB of any genotype, with positive HBsAg and HBeAg for >6 months prior to baseline, and detectable HBV DNA (>20,000 IU/mL) on at least 2 occasions, one month apart, within 42 days of baseline.

Compensated liver disease as evidenced by:

- Liver biopsy performed within 2 years prior to baseline showing no or minimal fibrosis (Liver Biopsy Scores [see Appendix 3]) and stable normal ALT levels (≤upper limit of normal [ULN] during the 6 months leading up to baseline (including two separate occasions at least 1 month apart over the 6 months prior to baseline).

OR

- Stable normal ALT levels (≤ULN), during the 1-year leading up to baseline (including three separate occasions at least 1 month apart over the 1 year prior to baseline) and no signs of HCC, advanced fibrosis/cirrhosis, or splenomegaly on liver abdominal ultrasound at screening.

Screening ALT was required to be normal (≤ULN).

Patients who had any previous anti-HBV treatment (including investigational treatments), or who were co- infected with hepatitis A virus (HAV), HCV, hepatitis D virus (HDV), HIV, or who had decompensated liver disease, advanced fibrosis or cirrhosis, or suspicion of HCC on ultrasound were excluded.

Assessment comment:

The inclusion and exclusion criteria were appropriate for the study design.

Sample size

Approximately 114 patients were planned to be recruited (57 per group) to ensure at least 50 evaluable patients in each group, providing a Fisher's Exact test with a two-sided 5% significance level with 80% power to detect a difference between treated and untreated groups (intention-to-treat (ITT) populations), based on the assumption of expected loss of HBsAg rates after 24 weeks after the end of treatment/end of untreated observation were 17% in the Pegasys® + lamivudine arm (D'Antiga *et al.*, 2006) and 0.6% in the untreated control group (Hsu, 1992).

Treatments

Group A: lamivudine or entecavir administered orally once daily given alone for 8 weeks then in combination with Pegasys® administered subcutaneously once weekly for 48 weeks.

Group B: untreated control.

Assignment to treatment arms was stratified by genotypes A vs B/C vs D/other and randomised 1:1. The choice of nucleoside analogue to be used in combination was made by the investigator prior to assignment to a treatment group, and the same nucleoside analogue continued throughout the treatment period.

Table 1. Pegasys® paediatric dosing regimen

Dose (μg)	BSA Range (m^2)
45	0.51–0.53
65	0.54–0.74
90	0.75–1.08
135	1.09–1.51
180	>1.51

Source: Protocol NV25361, Version 13, Table 1.

Table 2. Entecavir paediatric dosing regimen, patients aged 2 to <18 years

Body Weight [a]	Recommended Once Daily Dose of Oral Solution [b]
10.0 – 14.1 kg	4.0 mL
14.2 – 15.8 kg	4.5 mL
15.9 – 17.4 kg	5.0 mL
17.5 – 19.1 kg	5.5 mL
19.2 – 20.8 kg	6.0 mL
20.9 – 22.5 kg	6.5 mL
22.6 – 24.1 kg	7.0 mL
24.2 – 25.8 kg	7.5 mL
25.9 – 27.5 kg	8.0 mL
27.6 – 29.1 kg	8.5 mL
29.2 – 30.8 kg	9.0 mL
30.9 – 32.5 kg	9.5 mL
At least 32.6 kg	10 mL

[a] Body weight should be rounded to the nearest 0.1 kg

[b] Children with body weight at least 32.6 kg should receive 10 mL (0.5 mg) or oral solution or one 0.5 mg tablet once daily

Source: Protocol NV25361, Version 13, Table 2.

Paediatric lamivudine dose of 3-mg/kg/day (maximum of 100 mg daily).

Both entecavir and lamivudine were available as either oral solution or tablets, as appropriate for the individual dose/patient.

Assessment comment:

The study used standard recommended dosing of Pegasys®, lamivudine and entecavir as currently used for treatment of paediatric patients with chronic, immune-active hepatitis B. The duration of treatment was chosen based on that used in the two pilot studies where this treatment strategy first showed benefit (D'Antiga et al. 2006; Poddar et al. 2013).

Outcomes/endpoints

Primary efficacy endpoint

- Loss of HBsAg at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80).

Secondary efficacy endpoints

At 24 weeks post-treatment/endof untreated observation:

- Seroconversion to anti-HBs (loss of HBsAg and presence of anti-HBs)
- Seroconversion to anti-HBe (loss of HBeAg and presence of anti-HBe)
- Loss of HBeAg
- HBV DNA < 20,000 IU/mL, < 2000 IU/mL, undetectable and change from baseline (by PCR or hybridization)
- Combined endpoints: HBeAg seroconversion and HBV DNA < 20,000 IU/mL
- Combined endpoints: HBeAg seroconversion and HBV DNA < 2000 IU/mL

At 1-year post-treatment:

- Seroconversion to anti-HBs (loss of HBsAg and presence of anti-HBs)
- Seroconversion to anti-HBe (loss of HBeAg and presence of anti-HBe)
- Loss of HBsAg
- Loss of HBeAg
- HBV DNA < 20,000 IU/mL, < 2000 IU/mL, undetectable and change from baseline (by PCRor hybridization)
- Combined endpoints: HBeAg seroconversion and HBV DNA < 20,000 IU/mL
- Combined endpoints: HBeAg seroconversion and HBV DNA < 2000 IU/mL

Safety endpoints

At 24 weeks post-treatment/end of untreated observation:

- Incidence, nature, and severity of serious and non-serious adverse events (including neuropsychiatric assessment)
- Reasons for the discontinuation of any study medication

- Dose modifications for laboratory abnormalities and clinical adverse events
- Changes in vital signs and laboratory tests from screening/baseline, including thyroid function
- Effect on growth (height, weight and sexual maturity status)

At 1-year post-treatment:

- Incidence, nature, and severity of persisting adverse events, new-onset related serious adverse events/non-serious adverse events of special interest
- Changes in thyroid function from screening/baseline
- Effect on growth (height, weight and sexual maturity status)

AESIs were defined as:

- suspected transmission of an infectious agent by the study drug
- ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN or with clinical jaundice

Pharmacokinetic endpoints

- Samples collected from all treated patients for exploratory analysis.

Exploratory endpoints

- Quantitative HBsAg and quantitative HBeAg
- Presence of lamivudine or entecavir viral resistance
- Incidence of anti-drug antibodies from all patients treated with Pegasys® + lamivudine or Pegasys® + entecavir

Assessment comment:

The planned study endpoints were appropriate for the study objectives.

Statistical Methods

As enrolment into the study was terminated prematurely, the collected data were only descriptively summarised in the final CSR. No formal statistical hypothesis testing or formal treatment group comparisons were performed.

The number of observations, percentage of responders (response rate) and 95% CI (using the Clopper-Pearson method) for the response rate was presented for Groups A and B. AE summaries were presented for events with an onset date up to 24 weeks post treatment (follow-up Week 24)/end of untreated observation (Week 80) by group and for events with an onset at any time up to the end of the 1-year safety follow-up for the Pegasys® + lamivudine or entecavir treatment group. Laboratory data was descriptively summarised by treatment group over time.

Efficacy and safety data were presented as listings for Group C.

Individual and mean serum Pegasys® concentration versus time pharmacokinetic data was tabulated. Exploratory pharmacodynamic analyses were not covered in the Clinical Study Report.

Results

Recruitment/ Number analysed

At database lock (DBL) on 12 Mar 2020, 62 patients were enrolled into the study (Group A=26, Group B=33, Group C=3). The end of the study was defined as the date when the last patient, last visit (LPLV) for the final analysis occurred, which was 29 January 2020.

The region that recruited the highest number of patients randomized was Europe (48 patients), followed by North and South America (7 patients), Asia (3 patients) and Australia (1 patients).

Table 3. Patient disposition, all patients, study NV25361

Status	Group A PEG + LAM/ENT (N = 26)	Group B Untreated (N = 33)
Completed 8 weeks treatment/observation	26 (100.0%)	NA
Completed 20 weeks treatment/observation	26 (100.0%)	NA
Completed 32 weeks treatment/observation	26 (100.0%)	33 (100.0%)
Completed 44 weeks treatment/observation	26 (100.0%)	NA
Completed 56 weeks treatment/observation	26 (100.0%)	30 (90.9%)
Completed 80 weeks observation	NA	24 (72.7%)
Patients completed 56 weeks treatment/observation	26 (100.0%)	30 (90.9%)
Completed 4 weeks follow-up	25 (96.2%)	NA
Completed 24 weeks follow-up	25 (96.2%)	NA
Completed 1 year Long Term follow-up	25 (96.2%)	NA
Patients early discontinued from study treatment during treatment/observation	0	0
Completed 4 weeks follow-up	0	NA
Completed 24 weeks follow-up	0	NA
Completed 1 year Long Term follow-up	0	NA

(a) There is no visit at Follow up for patients in Group B,
The last visit for Patient 2950 was outside the visit window of week 80, however, the patient was considered to have completed the study.
NA: Not applicable.

Source: CSR Study NV25361 Table 1.

Withdrawal from the study for non-safety reasons was documented for 3/26 (11.5%) Group A and 8/33 (24.2%) group B, mainly for the reason of withdrawal by subject. No patients were prematurely discontinued from study treatment during the treatment/observation period. No patient was excluded from the ITT or safety populations.

Seven patients (26.9%) in Group A and 9 patients (27.3%) in Group B were considered to have at least 1 major protocol deviation during the study, mainly failure to fully meet study inclusion criteria with regards to baseline hepatic markers or HBV serology.

Baseline data

Baseline demographics were similar between Groups A and B. The ITT population was predominantly Asian or Caucasian, median age 12 years old in Group A and 11 years old in Group B, median body surface area (BSA) 1.4m^2 in both groups.

Baseline disease characteristics were similar between Groups A and B. The most frequent HBV genotype was D (Group A 40%, Group B 46.9%), followed by B, C and E. The mode of HBV acquisition was reported as perinatal in a high proportion of patients in both groups (73.1% in Group A and 69.7% in Group B). The most frequently reported fibrosis score was F1 (85.7% in Group A and 70% in Group B).

Patient exposure

The median exposure duration of Pegasys® was 48 weeks (range: 47 to 48 weeks) and the median number of doses was 48 (range: 43.0 to 48.0). The median cumulative dose was 6480.00 µg/mL (range: 3285.0 - 8640.0 µg/mL).

The median exposure duration of lamivudine was 56 weeks (range: 56 to 57 weeks) and the median number of doses was 387 (range: 375.0 - 395.0). The median cumulative dose was 38700.00 mg (range: 37500.0 - 39400.0 mg).

The median exposure duration of entecavir was 57 weeks (range: 56 to 58 weeks) and the median number of doses was 393 (range: 387.0 - 397.0). The median cumulative dose was 196.00 mg (range: 117.9 - 198.5).

Efficacy results

Primary efficacy endpoint

Table 4. HBsAg loss at 24 Weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80): ITT Population

Group A PEG + LAM/ENT (N= 26) (95% CI) (a)	Group B Untreated (N= 33) (95% CI) (a)
1 (3.8%) (0.10%,19.64%)	0 (0.0%) (0.00%,10.58%)

(a) 95% Confidence Interval of response rate is calculated by Clopper-Pearson method.
(b) Missing values are treated as non-responders.

Source: CSR Study NV25361 Table 7.

In Group C, 0/3 patients demonstrated loss of HBsAg at 24 weeks post-treatment.

Secondary efficacy endpoints

Table 5. Responses at 24 Weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80): ITT Population

	Group A PEG + LAM/ENT (N= 26) (95% CI) (a)	Group B Untreated (N= 33) (95% CI) (a)
Seroconversion to anti-HBs	1 (3.8%) (0.10%,19.64%)	0 (0.0%) (0.00%,10.58%)
Seroconversion to anti-HBe	0 (0.0%) (0.00%,13.23%)	3 (9.1%) (1.92%,24.33%)
Loss of HBeAg	1 (3.8%) (0.10%,19.64%)	4 (12.1%) (3.40%,28.20%)
HBV-DNA < 20000 IU/mL	2 (7.7%) (0.95%,25.13%)	4 (12.1%) (3.40%,28.20%)
HBV-DNA < 2000 IU/mL	2 (7.7%) (0.95%,25.13%)	4 (12.1%) (3.40%,28.20%)
HBV-DNA undetectable(b)	0 (0.0%) (0.00%,13.23%)	2 (6.1%) (0.74%,20.23%)
HBeAg seroconversion and HBV-DNA < 20000 IU/mL	0 (0.0%) (0.00%,13.23%)	3 (9.1%) (1.92%,24.33%)
HBeAg seroconversion and HBV-DNA < 2000 IU/mL	0 (0.0%) (0.00%,13.23%)	3 (9.1%) (1.92%,24.33%)

(a) 95% Confidence Interval of response rate is calculated by Clopper-Pearson method.
(b) HBV-DNA undetectable is defined as HBV-DNA < 29 IU/mL as per HBV polymerase chain reaction (PCR) by Roche Taqman.
(c) Missing values are treated as non-responders.

Source: CSR Study NV25361 Table 8.

Table 6. Responses at 1 year post-treatment, Group A: ITT Population

	Group A PEG + LAM/ENT (N= 26) (95% CI) (a)
Seroconversion to anti-HBs	1 (3.8%) (0.10%,19.64%)
Seroconversion to anti-HBe	2 (7.7%) (0.95%,25.13%)
Loss of HBeAg	3 (11.5%) (2.45%,30.15%)
Loss of HBsAg	1 (3.8%) (0.10%,19.64%)
HBV-DNA < 20000 IU/mL	4 (15.4%) (4.36%,34.87%)
HBV-DNA < 2000 IU/mL	2 (7.7%) (0.95%,25.13%)
HBV-DNA undetectable(b)	0 (0.0%) (0.00%,13.23%)
HBeAg seroconversion and HBV-DNA < 20000 IU/mL	2 (7.7%) (0.95%,25.13%)
HBeAg seroconversion and HBV-DNA < 2000 IU/mL	2 (7.7%) (0.95%,25.13%)

(a) 95% Confidence Interval of response rate is calculated by Clopper-Pearson method.
(b) HBV-DNA undetectable is defined as HBV-DNA < 29 IU/mL as per HBV polymerase chain reaction (PCR) by Roche Taqman.
(c) Missing values are treated as non-responders.

Source: CSR Study NV25361 Table 9.

In Group C, 2/3 patients demonstrated seroconversion to HBeAb and loss of HBeAg at 1 year post-treatment.

Spontaneous HBeAg loss in chronically infected children occurs at an annual rate of 10% -16% (Bortolotti et al. 1986; Moyes et al. 1993), whereas spontaneous loss of HBsAg is as low as 0.6% per year (Hsu et al. 1992), the children achieving earlier seroconversion being those with biochemical and/or histological evidence of active disease. Moreover, the annual HBsAg clearance rate is significantly higher in those children who are already anti-HBe positive (i.e., low viral load) than in those with HBeAg (i.e., high viral load) (1.7% vs. 0.4%).

Assessment comment:

The small sample size and premature termination of the study preclude statistical comparison of the groups, but the frequency of attainment of virological endpoints seen across the three groups is consistent with background annual spontaneous seroconversion rates previously reported in untreated paediatric patients. Long-term follow-up studies in children show that many seroconvert from HBeAg to anti-HBe before reaching adulthood and most of those children have stable remission with normal ALT thereafter.

Safety results

Table 7. Overview of Adverse Events up to 24 weeks post-treatment/end of untreated observation: Safety Population

	Group A PEG + LAM/ENT (N = 26)	Group B Untreated (N = 33)
Total number of patients with at least one AE	24 (92.3%)	15 (45.5%)
Total number of AEs	269	26
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients with at least one Serious AE	0	1 (3.0%)
AE leading to withdrawal from treatment	0	0
AE leading to dose modification/interruption	3 (11.5%)	0
AE related to study treatment	19 (73.1%)	0
Severe AE (at greatest intensity)	1 (3.8%)	1 (3.0%)
Non-serious AE of special interest	0	0

Source: CSR Study NV25361 Table 10.

Table 8. Adverse Events by Preferred Term, Relative Frequency ≥5% (up to 24 weeks post-treatment/end of untreated

MedDRA Preferred Term	Group A PEG + LAM/ENT (N=26)	Group B Untreated (N=33)
Total number of patients with at least one adverse event	24 (92.3%)	15 (45.5%)
Total number of events	269	26
HEADACHE	14 (53.8%)	0
PYREXIA	11 (42.3%)	0
FATIGUE	5 (19.2%)	0
NAUSEA	4 (15.4%)	0
ABDOMINAL PAIN UPPER	3 (11.5%)	2 (6.1%)
DIZZINESS	3 (11.5%)	0
EPISTAXIS	3 (11.5%)	1 (3.0%)
NASOPHARYNGITIS	3 (11.5%)	1 (3.0%)
PAIN	3 (11.5%)	0
VOMITING	3 (11.5%)	1 (3.0%)
ACNE	2 (7.7%)	0
ALOPECIA	2 (7.7%)	0
ASTHENIA	2 (7.7%)	0
CONTUSION	2 (7.7%)	0
DECREASED APPETITE	2 (7.7%)	0
ECZEMA	2 (7.7%)	0
GASTROENTERITIS	2 (7.7%)	0
HYPERTHERMIA	2 (7.7%)	0
INJECTION SITE BRUISING	2 (7.7%)	0
LIMB INJURY	2 (7.7%)	0
MIGRAINE	2 (7.7%)	0
MYALGIA	2 (7.7%)	0
PAIN IN EXTREMITY	2 (7.7%)	1 (3.0%)
UPPER RESPIRATORY TRACT INFECTION	2 (7.7%)	1 (3.0%)
INFLUENZA	1 (3.8%)	2 (6.1%)

Investigator text for AEs encoded using MedDRA version 22.1.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once.

Source: CSR Study NV25361 Table 11.

Adverse events

In Group A, general disorders and administration site conditions was the most common SOC, specifically PTs of pyrexia, fatigue and pain in 3 children. Nervous system disorders was the next most common SOC, specifically PTs of headache and dizziness.

The majority of reported AEs were of mild or moderate intensity, except one patient in Group A reporting severe events of migraine (on study Day 57), night sweats (on study Day 107) and headache (on study Day 338) and one patient in Group B reporting severe events of dehydration and pharyngitis.

One patient in untreated Group B (3%) reported 2 serious AEs (pharyngitis and dehydration). There were no other SAEs or deaths. There were no AESIs. None of the patients were discontinued from any of the study treatments due to adverse events.

Pegasys® dose modifications due to AEs or laboratory abnormalities were reported in 6 patients (23%) in Group A. Three patients (12%) reported AE (tooth abscess, alanine aminotransferase increased, neutropenia), and 4 reported non-AE laboratory abnormalities (2 low absolute neutrophil count (one also reported as AE), 2 elevated serum ALT, 8% each).

Laboratory values

Haematology

Low white blood cell (WBC) count occurred at any time post-baseline in 24/26 (92.3%) of Group A and 3/33 (9.7%) of Group B. Most abnormalities were either Grade 1 or 2 according to the Division of Aids Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS), however in Group A 2 patients experienced Grade 3 low WBC and one patient reported neutropenia as an AE.

Chemistry

High laboratory values occurring at any time post-baseline were more frequent in Group A than Group B with regard to ALT (84.6% vs 22.6%), AST (69.2% vs 9.7%), GGT (50.0% vs 3.2%) and INR (26.9% vs 16.1%). Low glucose values occurring at any time post-baseline were more frequent in Group A than Group B (20.8% vs 4.0%). High uric acid values occurring at any time post-baseline were more frequent in Group B than Group A (12.0% vs 4.2.%).

Abnormally high (DAIDS Grade ≥3) values occurring post-baseline were reported for the following biochemistry parameters: In Group A, high ALT of Grade 3 (4 patients, 15.4%) and Grade 4 (1 patient, 3.8%), high AST of Grade 3 (2 patients, 7.7%), low glucose of Grade 3 (2 patients, 8.3%), high uric acid of Grade 3 (1 patient, 4.2%). In Group B, high uric acid of Grade 3 was reported in 3 patients (12%).

In Group A, mean (SD) change from baseline for thyroid stimulating hormone (TSH) was -0.21 (0.76) and -0.46 (0.65) at Week 56 and 1-year follow-up, respectively. In Group B, mean (SD) change from baseline for TSH was 0.19 (1.01) and 0.23 (0.66) at Week 56 and Week 80, respectively. There were no clinically relevant changes from baseline in triiodothyronine (T3) and thyroxine (T4) levels observed in either of the groups.

Vital signs

One patient in Group A (3.8%) experienced high diastolic blood pressure (>20% increase from baseline). Two patients in Group B (6.1%) reported low pulse rate (>20% decrease from baseline). No associated AE was reported. No clinically significant trends were observed in either group in changes from baseline over time in SBP, DBP, pulse rate, or mean temperature.

Neuropsychiatric assessments

Total T-score in the Child Depression Inventory (CDI) for Group A remained close to baseline values throughout the study and showed no relevant changes over time post baseline up to week 4 of initial follow-up. The CDI was not administered in post-baseline visits in Group B. In Group A, one patient reported an adverse event of depressed mood of mild intensity, and the total CDI score was between 0-3 throughout the study.

Height and weight

At Week 56, the proportion of patients with >15% drop in height-for-age percentile from baseline was 3.8% in Group A and 4.5% in Group B. In Group A, follow-up at Week 24 (24 patients) and 1-year (24 patients), these proportions changed to 12.5% and 20.8% respectively. At Week 80 in Group B, the proportion of patients with >15% drop in height-for-age percentile from baseline was 16%.

At Week 56, the proportion of patients with >15% drop in weight-for-age percentile from baseline was 34.6% in Group A and 4.5% in Group B. In Group A, follow-up at Week 24 (25 patients) and 1-year (24 patients), these proportions changed to 20% and 25% respectively. At Week 80 in Group B, the proportion of patients with >15% drop in weight-for-age percentile from baseline was 12%.

Assessment comment

The reported adverse events and frequencies are in keeping with the known safety and tolerability profile of the treatments used in the study, with the most common being non-specific/systemic AEs of headache, pyrexia, fatigue and nausea. Low WBC count, abnormal LFTs, and low serum glucose occurred more frequently in Group A and are known to occur in association with one or more of the treatments used in the study.

The difference in weight loss amongst Group A vs Group B patients at week 56 is striking, although it must be remembered that the sample size is small. Around one third of patients in Group A experienced a weight-for-age percentile drop >15% by week 56 on treatment, and this despite the fact that height-for-age percentile drop was only modest in both groups by week 56. Also significant is that lamivudine, which was co-administered to some patients in Group A, is known to cause weight gain, and therefore would be expected to have some counter effect.

The CSR states that, due to lack of long-term follow-up data and limited sample size resulting from early termination of enrolment, it is difficult to draw any conclusion regarding whether there was long-term growth inhibition in children treated with PEG + LAM/ENT (Group A). On-treatment growth inhibition with Pegasys®-containing regimens has been observed in previous studies of paediatric patients, however the majority of patients returned to their baseline height for age percentile within 5 years of post-treatment follow-up. The current SmPC contains a warning regarding the potential impact on growth and development in children.

Pharmacokinetic results

Table 9. Summary of serum Pegasys® RO0258310 concentrations by visit

Analyte: RO0258310 (pg/mL) Treatment: PEG + LAM/ENT

Visit/Timepoint	Nominal Time (day)	n	Number of LTRs	Mean	SD	CV % Mean	Geometric Mean	CV % Geometric Mean	Median	Minimum	Maximum
BASELINE PREDOSE	0	0	10		NE	NE	NE		NE	NE	NE
WEEK 12 PREDOSE	84	6	2	8430	6090	72.2	5160	241	8810	425	15400
WEEK 16 PREDOSE	112	8	1	16300	10100	61.9	11000	195	18700	667	28700
WEEK 20 PREDOSE	140	10	1	13800	8740	63.4	9850	150	13600	733	30100
WEEK 32 PREDOSE	224	11	1	14900	7710	51.8	12000	98.5	15100	1480	28000
WEEK 32 24H-48H POST-DOSE	225	8	0	22700	6070	26.8	21800	31.2	23000	11600	31900
WEEK 32 72H-96H POST-DOSE	227	8	0	23000	4900	21.3	22600	22.8	23500	15700	29400
WEEK 32 168H POST-DOSE	231	6	0	19300	5880	30.4	18700	26.8	17400	15200	30800
WEEK 44 PREDOSE	308	9	0	21900	14200	64.8	13800	287	22000	315	48500
WEEK 56 PREDOSE	392	7	0	25400	13100	51.8	21600	79.2	23900	5040	50000

CV = coefficient of variation; LTR = lower than reportable; NE = not evaluable;
NR = non-Reportable. LTR results at nominal time <=0 are set to 0,
For a given treatment and sampling time point: If one-third or fewer values were LTR, then all summary statistics are reported. If more than one-third values were LTR, only the median and maximum are reported, geometric mean is reported if non-zero values and other statistics are displayed as NR.

Source: CSR Study NV25361 appendices.

2.3.3. Discussion on clinical aspects

Study NV25361 was a Phase 3 study aimed to evaluate the efficacy and safety of treating children with immune-tolerant CHB with Pegasys® in combination with either lamivudine or entecavir, with therapy duration based on those used in two pilot studies where this particular treatment strategy was first tested. The study design was appropriate for the original objectives. However, during the course of the study, results from two multicentre NIH trials demonstrated minimal to no efficacy of the same intervention in both adult and paediatric patient populations with immune-tolerant CHB. Based on these results, it was decided that the benefit-risk balance had changed and recruitment to Study NV25361 was terminated prematurely. The study was also removed from the PIP commitments and the RMP.

The applicant has hereby submitted the results of the prematurely terminated study. Only 62 patients were enrolled into the study (Group A=26, Group B=33, Group C=3). The collected data were only descriptively summarised in the final CSR. No formal statistical hypothesis testing or formal treatment group comparisons were performed.

Overall, 1/26 patients (3.8%) in the treatment group PEG + LAM/ENT (Group A) and no patients from untreated group (Group B) had HBsAg loss at 24 Weeks post-treatment or end of untreated observation (Week 80), respectively. Responses of secondary efficacy endpoints at 24 or 52 weeks post-treatment/end of untreated observation, respectively, were similar to the primary efficacy observations. In patients in the Pegasys® monotherapy arm from the earlier study protocol (Group C), 2/3 patients demonstrated seroconversion to HBeAb and loss of HBeAg at 1-year post-treatment. The small sample size and premature termination of the study preclude statistical comparison of the groups, but in absolute numbers the rate of antigen loss and seroconversion is very low across all three groups, and consistent with background annual spontaneous seroconversion rates previously reported in untreated paediatric patients.

The adverse events and deviations in laboratory values reported by patients in the treatment group PEG + LAM/ENT (Group A) during the study are in keeping with the known safety and tolerability profiles of the individual components of the treatment regimen. Although comprehensive assessment is not possible due to the small sample size and limited follow up time, the data are suggestive of an on-treatment impact of Pegasys® + LAM/ENT on growth, which has previously been described in earlier studies and is listed as a warning in the SmPC for Pegasys®. There were no unexpected safety issues.

The reason for the disparity between results of the initial pilot studies and subsequent larger clinical trials is not clear. Long-term follow-up studies have shown that more than 80% of Caucasian children with HBV infection seroconvert from HBeAg to anti-HBe before reaching adulthood. Lower figures are reported in Asian children, possibly due to the fact that perinatal transmission is the dominant route of infection in this area. The annual spontaneous HBeAg seroconversion rate is up to 14-18% in Caucasian children vs less than 2% in Asian children below 3 years of age. It is interesting that in one of the two positive pilot studies (D'Antiga et al. 2006) the response rate appeared to be highest amongst Asian patients vs European patients. The other pilot study (Poddar et al. 2013) was conducted in India. Similarly, in their discussion of the results of the NIH clinical study in paediatric patients with immune-tolerant CHB (Rosenthal et al., 2019), the authors note that the trial's only two complete responders were Asian (both suspected mother to child transmission; one genotype B and one genotype C), while two patients with incomplete virologic response were Asian (genotype B) and Black (genotype E). They postulate that differences might exist in response rate between different biral viral genotypes and/or different ethic groups. However, in the NIH clinical study in adult patients with immune-tolerant CHB (Feld et al. 2019), in which 96% of enrolled patients were Asian (almost exclusively genotypes B and C), no patient met the primary endpoint of both HBeAg loss and HBV DNA ≤1000 IU/mL 48 weeks after treatment ended. The data presented in the submitted CSR for Study NV25361 are not sufficiently detailed to allow for consideration of virological outcomes vs viral genotype or ethnicity.

3. Overall conclusion and recommendation

Results from the prematurely-terminated Phase 3 Study NV25361 of Pegasys® in combination with either lamivudine or entecavir for treatment of children with immune-tolerant chronic hepatitis B, though limited and only descriptive in nature, appear to support the conclusion of two multicentre NIH trials demonstrated minimal to no efficacy of the intervention in immune-tolerant CHB. In some instances, it is considered valuable to the prescriber to include negative study results relevant to the paediatric population in the SmPC, for example where a treatment authorised for a particular indication

in adults has not been shown effective for the same indication in children. However, in this case there is no expectation of a future indication of treatment of immune-tolerant CHB in adults, and the published evidence for overall lack of efficacy in immune-tolerant CHB is expected to be familiar to clinicians experienced in initiating treatment of CHB, therefore additions to the efficacy information in the currently approved Product Information are not warranted.

No new safety concerns were identified during the course of prematurely-terminated Study NV25361. Long-term data on growth, thyroid effects and neuropsychiatric events in paediatric patients continue to be collected as part of the 5-year follow up of patients in ongoing study YV25718 in the paediatric population with immune-active CHB. No update to the safety information in the currently approved Product Information is necessary at this time.

☒ Fulfilled:

PAM fulfilled. No regulatory action required.