

Telbivudine/Torcitabine Idenix/Novartis

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Idenix (formerly Novirio) and Novartis are developing two β -L-deoxynucleosides, telbivudine and torcitabine, for the potential treatment of hepatitis B virus infection. Phase III trials of telbivudine were underway by August 2002 and phase I/II trials of the torcitabine prodrug, valtorcitabine, were ongoing in November 2003.

Introduction

There are approximately 400 million people worldwide with chronic hepatitis B virus (HBV) infection, about one-third of whom have potentially progressive and life-threatening liver disease associated with the infection. Chronic hepatitis B infection can lead to cirrhosis, liver failure and hepatocellular carcinoma. Globally, HBV infection accounts for over one million deaths annually [433880]. At present, lamivudine and adefovir dipivoxil are the only approved nucleoside/nucleotide analogs for the treatment of HBV infection. However, resistance to lamivudine is now recognized in 16 to 32% of HBV-infected patients after the first year of monotherapy [397171], [458973], and approximately 50% of patients after two years [488843]. With adefovir treatment, the resistance rate is much lower, at approximately 2.5% after two years of therapy [488843]. Experience with treating chronic HIV infections has proven the advantage of therapy with a combination of antiviral compounds. Similarly for HBV, there is a clear need for additional antiviral compounds. Several promising candidates are currently in clinical development.

Idenix (formerly Novirio) discovered that the known β -L-nucleosides, L-dA, L-dC (torcitabine) and L-dT (telbivudine), have highly specific activity against HBV [397171]. These L-nucleosides are essentially without activity against any of the other viruses tested and are similarly without effect in cell culture and *in vivo* toxicological tests. However, they are phosphorylated within human cells to their triphosphates which inhibit the HBV DNA polymerase, but not human polymerases [397171], [458973].

Of these three compounds, telbivudine was the only compound to combine reasonable oral bioavailability with good anti-HBV activity and was therefore progressed with the highest priority. Torcitabine was being progressed as its di-valinyl ester prodrug (val-L-dC), which improves its oral bioavailability by approximately 4-fold. However, during the phase I/II, dose-escalation study, therapy was switched to the 3'-mono-valinyl-L-dC (valtorcitabine). L-dA appears to be less active than the other two compounds and therefore some particular property will need to be identified if it is to be progressed.

This evaluation covers all the above compounds.

Originator Idenix Pharmaceuticals Inc (formerly Novirio Pharmaceutical Ltd)

Licensee Novartis Pharma AG

Licensee for telbivudine Sumitomo Pharmaceuticals Co Ltd

Status of telbivudine Phase III Clinical

Status of torcitabine Phase II Clinical

Indication Hepatitis B virus infection

Action Viral replication inhibitor

Biotechnology Nucleoside (and derivatives), Oral formulation

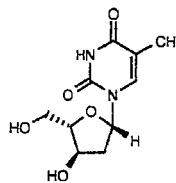
Synonyms and analogs for telbivudine anti-HBV L-nucleosides, L-2-deoxythymidine, L-dT, LDT-600, β -L-thymidine, NV-02B, NV-02 program

Synonyms and analogs for torcitabine 3',5'-divalanyl-L-dC, LDC-300, L-dC, L-dC prodrug, L-2-deoxycytidine, β -L-2'-deoxycytidine, 3'-mono-valinyl-L-dC, NV-02C, val-L-dC, valtorcitabine

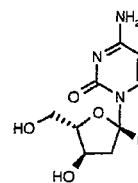
Synonym for L-dA L-2-deoxyadenosin

CAS for telbivudine 2,4(1*H*,3*H*)-Pyrimidinedione, 1-(2-deoxy- β -L-erythro-pentofuranosyl)-5-methyl-
Registry No: 3424-98-4

CAS for torcitabine 2(1*H*)-Pyrimidinone, 4-amino-1-(2-deoxy- β -L-erythro-pentofuranosyl)-
Registry No: 40093-94-5



telbivudine



torcitabine

Synthesis and SAR

The L-nucleosides closely resemble the natural deoxynucleosides, except in the spatial arrangement of the base and sugar moieties having the L- rather than the D-configuration: just as a left hand is similar to, but not identical to, the right hand.

For the synthesis of telbivudine and torcitabine, two strategies were used: initially the method of Holy [505622] was followed, which was then modified to give the target compounds (in 20 g quantities) in six and seven steps, respectively [364588], [513833]. Currently, telbivudine and valtorcitabine are synthesized on a much larger scale by unpublished methods [G Gosselin (University of

Montpellier, France), personal communication]. L-dA was obtained by a six-step synthesis yielding 20 g of the compound [364575].

In SAR studies [460857], the hydroxyl group in the 3'-position was shown to be the key to the highly specific activity against HBV. Other compounds either lacked activity against HBV or had activity against both HBV and HIV. To further assess their specificity, torcitabine, telbivudine and L-dA were tested against a panel of 15 RNA and DNA viruses. They were active only against the hepadnaviruses HBV and the closely related duck (DHBV) and woodchuck (WHBV) hepatitis virus [460857]. Clearly the hope is that these compounds, having such great specificity for only one virus, will lack toxic effects in human cells.

Preclinical Development

In the primary screen for human HBV, the HepG 2.2.15 cell culture assay, the activities of telbivudine and torcitabine were more consistent than the activity of L-dA. EC_{50} values (μ M) were 0.19 ± 0.09 and 0.24 ± 0.08 for telbivudine and torcitabine, respectively, but given as a range of 0.1 to 1.9 for L-dA [397171]. All three compounds were active against the closely related DHBV in primary duck hepatocytes ($EC_{50} = 0.2, 0.9$ and 0.2μ M for telbivudine, torcitabine and L-dA, respectively) [460857].

Additional cell culture studies have shown that combinations of telbivudine and torcitabine are synergistic [405816]. In HepG 2.2.15 cells, their EC_{50} values were 1.2 and 1.1 μ M, respectively; combined in the ratios 1:1, 1:3 and 3:1, the EC_{50} values were 0.30, 0.33 and 0.41 μ M, respectively [R Boehme, personal communication]. In a cell culture study on cross resistance, viruses encoding the rtM204I (formerly known as M552I) and rtL180M (formerly known as L528M) polymerase mutations, and known to be highly resistant to lamivudine [513706], were also resistant to telbivudine (IC_{50} values increased > 235- and > 132-fold, respectively) [458975].

As a model for chronic human HBV infection, chronically infected woodchucks have been used widely. Three studies have been completed by Tennant *et al* in this model [397171], [460857], [519625], [R Boehme, personal communication]:

(i) Telbivudine versus torcitabine, dosing at 10 mg/kg daily for 4 weeks ($n = 3$ animals/group), limit of detection of WHBV DNA was 300 genome equivalents/ml.

(ii) Telbivudine versus torcitabine versus telbivudine + torcitabine, each at 1 mg/kg daily (low dose to explore synergy) for 12 weeks ($n = 3$ animals/group), limit of detection of WHBV DNA was 300 genome equivalents/ml.

(iii) Telbivudine (10 mg/kg daily) versus val-L-dC (10 mg/kg daily) versus lamivudine (15 mg/kg daily) versus combinations of telbivudine + lamivudine or val-L-dC (each at the same dose as monotherapy) versus placebo, for 12 weeks ($n = 5$ animals/group), limit of detection of WHBV DNA was 30 genome equivalents/ml.

In the first study, levels of WHBV DNA were measured during the 4 weeks of treatment and for 8 weeks afterwards.

Telbivudine was the most active compound in this model. WHBV DNA levels were reduced by up to 8 \log_{10} copies/ml (log) during the treatment period, but returned to pre-treatment levels by 4 to 8 weeks later [397171], [460857]. In torcitabine-treated animals, the decrease in WHBV DNA was from 2 to 6 log with rebound within a week of ending treatment. Considering that torcitabine is poorly absorbed, a prodrug may be expected to give a better result. In a similar study with L-dA, there was only a modest decrease in WHBV DNA levels (approximately 1.5 log) followed by a rapid return to baseline levels [397171]. All three compounds were well tolerated and caused no drug-related toxicity [397171], [460857].

The second study was to investigate synergy. Telbivudine and torcitabine were used at only 1 mg/kg (each alone versus the two combined), but the treatment period was for 12 weeks. At this low dose, torcitabine alone was inactive. By the end of the therapy with telbivudine alone and in combination with torcitabine, the WHBV DNA levels were reduced by approximately 5 and 7 log, respectively [R Boehme, personal communication]. The addition of torcitabine, although inactive by itself, had given a further 2-log reduction in WHBV DNA levels. The synergistic effect may have been greater had equi-active doses of telbivudine and torcitabine been used. Brief summaries have been published [405816], [460857].

These two studies demonstrate that, in those treated animals that had the best reductions of WHBV DNA levels, there was a marked reduction of WHBV surface antigen, although the effect was delayed relative to the viral DNA levels. Also, a prolonged time before viral rebound was observed [460857].

In the third and largest study, two combinations of telbivudine (with val-L-dC and lamivudine) were evaluated. In comparing the activity of telbivudine against that of lamivudine in this woodchuck model, one should be aware that lamivudine is less well absorbed and less efficiently converted to its active triphosphate form in woodchucks relative to humans [397171]. Nevertheless, the results were impressive. At 4 weeks, one out of five telbivudine-treated animals had undetectable WHBV DNA levels (> 10 log reduction) and the other four animals had 5- to 7-log reduction in their viral DNA levels. When combined with val-L-dC, at 4 weeks, there was a reduction in viral DNA levels of > 7 log in one out of five animals and > 10 log in the other four animals. By 12 weeks, all five animals had viral DNA levels below the limit of detection (> 10 log reduction) [R Boehme, personal communication]. With lamivudine alone, viral DNA levels were reduced by 1 to 5 log; combination with telbivudine did not appear to add to the efficacy of telbivudine alone [519625], [R Boehme, personal communication].

Metabolism and Pharmacokinetics

Telbivudine was well absorbed in cynomolgus monkeys, oral bioavailability being 69% (which compares with 38% in woodchucks). However, the rate of absorption was slow in both monkeys and woodchucks (T_{max} from 1 to 4 h) and the plasma terminal half-life ($t_{1/2}$) was approximately 1.5 h (for monkeys) and approximately 3.5 h (for woodchucks)

[460857]. If telbivudine itself were the active moiety, then the short plasma half-life would indicate that several doses per day would be required. However, telbivudine is taken into cells and readily phosphorylated to its triphosphate (L-dTTP), the active form that inhibits HBV DNA polymerase. The triphosphate is trapped within the cell and has a half-life of at least 15 h in HepG2 and primary human hepatocytes. The long half-life of the active form suggests that once-daily dosing should be possible [458973].

The oral bioavailability of torcitabine is markedly less than that of telbivudine. In cynomolgus monkeys and woodchucks, the bioavailability is approximately 16 and 10%, respectively [460857]. This low oral bioavailability prompted the search for prodrugs with more favorable profiles [406019]. The 3',5'-divalinaline ester of torcitabine (val-L-dC) has much improved absorption and is converted efficiently to torcitabine (bioavailability of torcitabine is approximately 70% in monkeys) [460857]. The C_{max} and AUC for torcitabine achieved with orally administered val-L-dC were significantly greater (2.5- to 5-fold) than those obtained from an equivalent dose of torcitabine [405819]. The improved pharmacokinetics, combined with its ease of synthesis [406020] led to the selection of the divalinaline ester as the prodrug for torcitabine. However, during phase I/II trials, the divalinaline ester was later replaced by the 3'-monovalinaline ester (valtorcitabine) [R Boehme, personal communication], which gives 84% bioavailability of torcitabine in monkeys [513833].

The cellular pharmacology of the nucleoside analogs was determined in HepG2 cells and primary human hepatocytes. Like telbivudine, torcitabine is efficiently phosphorylated to its active triphosphate form within human cells and it has a similar, long half-life (approximately 15 h). In addition, torcitabine is metabolized to L-dUTP, via the action of deoxycytidylate deaminase on L-dMP, and to L-dCDP-choline [460857]. As L-dCTP is formed in higher concentrations than L-dUTP, and is also the more active inhibitor of WHBV polymerase, it seems that L-dCTP is the more important metabolite for activity [397171], [458973]. Exposure of HepG2 cells to telbivudine and torcitabine together led to concentrations of activated metabolites similar to those achieved with either agent alone [458973]. L-dTTP and L-dCTP were not substrates for human DNA polymerases α , β or γ up to 100 μ M [397171].

L-dA is reported to be well absorbed and efficiently converted to its triphosphate (L-dATP) which inhibits WHBV DNA polymerase at approximately 1 μ M. However, further data on its metabolism are not available [397171], [458973], [460857].

Toxicity

For telbivudine, toxic effects have not been observed in any studies [406048], [460857]. Except for the carcinogenicity studies in mice and rats, which are still ongoing, most of the preclinical toxicity testing has been completed.

Telbivudine and torcitabine lacked cytotoxicity in animal and human primary cells (at 1000 μ M) and bone marrow progenitor cells (at 50 μ M), exhibited no mitochondrial

toxicity or incorporation into mitochondrial or cellular DNA, did not inhibit human cellular DNA polymerases (as their triphosphates at 100 μ M) and were non-mutagenic [364489], [397171], [460857], [462644].

In vivo toxicology data for telbivudine revealed essentially no toxicity in doses up to 2 g/kg daily for 6 and 9 months in rats and monkeys, respectively [435422]. Acute toxicity studies in rats and monkeys showed that animals given the drug at 2 g/kg daily for 28 days exhibited no overt signs of illness, organ pathology, or hematological problems. No macroscopic lesions attributable to telbivudine were observed at necropsy, nor were there any microscopic findings considered to be related to the compound [460857]. Chronic dosing of 1 g/kg daily for 6 months led to no adverse effects. Mutagenic evaluations (Ames, chromosome aberration and other tests) were negative [406048], [406913].

For torcitabine and valtorcitabine, much of the preclinical toxicology program is still to be completed. So far, minor hematological effects were reported with torcitabine in sub-chronic toxicology (in rats and monkeys) tests [513826].

Clinical Development

Phase III

Telbivudine was evaluated in a randomized, placebo-controlled, dose-escalation study [513820]. Dosing was once daily for 4 weeks starting at 25 mg and doubling up to 800 mg ($n = 7$ patients/cohort which included one patient on placebo). After treatment, there was a 12-week observation period. Although the small number of patients per group may account for the apparent inconsistencies between efficacies of similar doses, the trends were clear. All doses were effective with the levels of HBV DNA reduced by 2.5 and 3.8 log for the lowest and highest doses, respectively. At all doses, the HBV DNA levels returned to baseline, but there was a trend towards a slower return with the highest doses. All doses were well tolerated. This was an encouraging start as previously reported drugs, lamivudine (3TC, the current standard therapy), adefovir dipivoxil (approved by the FDA in late 2002), entecavir (being developed by Bristol-Myers Squibb Co), emtricitabine and clevudine (both from Gilead Sciences Inc), all reduced viral DNA levels by less than 3 log at 4 weeks [513850]. Calculating the half-life of HBV-infected cells seems to give the clearest indication of telbivudine dose response; even the 800-mg dose may not give the maximal response [513820]. For further evaluation in phase IIb studies, 400- and 600-mg doses were chosen.

A similar 28-day, dose-escalation trial was planned for val-L-dC, but with doses ranging from 50 to 1200 mg daily. Thus far, results for doses up to only 400 mg (equivalent to approximately 170 mg active drug) have been reported. HBV DNA was reduced by 1 log for the 50-mg dose and by 2 log for the 400-mg dose [519344]. However, during this study it was noted that the mono-ester (3'-valinyl-L-dC) was less hygroscopic, more stable and had similar bioavailability in humans. Supplies of the divalinaline ester were therefore converted to the 3'-mono-valinyl ester for continuation of this clinical trial. In the fourth quarter of 2002, the decision was taken to develop torcitabine as its 3'-mono-valinyl ester

which was assigned the name valtorcitabine [R Boehme, personal communication].

Phase IIb

Therapy of HBV requires long-term treatment of usually a year or more. Therefore, to minimize the risk of selecting drug-resistant virus strains, combinations of drugs are expected to be used, just as for HIV therapy. Therefore, even in this early phase of the clinical trial program, telbivudine is being tested alone and in combination with lamivudine. In a randomized, placebo-controlled trial in hepatitis B e antigen (HBeAg)-positive patients with compensated chronic hepatitis B (n = 20 patients/group), telbivudine (400 or 600 mg) was compared with lamivudine (100 mg) alone and in combination (using the same doses as for monotherapies); all drugs were administered once daily for 52 weeks. The analyses at 12 and 24 weeks have been completed and some results at 52 weeks have just been presented [513844], [513846]. The primary efficacy parameter is the reduction (log) of HBV DNA levels (limit of quantitation = 200 copies/ml). Lamivudine alone at 24 weeks (4.7 log), demonstrated little change from 12 weeks. In contrast, with all four telbivudine-containing regimens, there was a continuing reduction in HBV DNA levels so that by 24 weeks both telbivudine only groups had reductions of 6.1 log, and the combination groups by 6.2 log. Both these results were significantly better than for lamivudine alone (p = 0.05 and 0.01, respectively). The percentages of patients negative for HBV DNA by PCR at 24 weeks were 16, 32 and 32% for lamivudine and telbivudine alone and combination groups, respectively. Alanine aminotransferase (ALT) normalizations were similar in all groups (approximately 75% of patients at 24 weeks) [513850].

At 52 weeks, the mean reductions in HBV DNA levels were maintained [513844], [513846]; lamivudine (4.6 log), mean for both telbivudine only groups (6.1 log), and combination groups (6.0 log) (p < 0.05 for telbivudine groups versus lamivudine). The proportions of patients having undetectable HBV DNA by PCR were 32, 61 (p < 0.05 versus lamivudine) and 49% for the same groups, respectively. Those with HBeAg loss (all but one patient seroconverted) were 28, 33 and 17%, respectively. ALT normalizations were 63, 86 (p < 0.05 versus lamivudine) and 78%, respectively. The proportions of virus breakthrough were 21, 5 and 12%, respectively. Of these, the majority (virus from two, two and three patients, respectively) had a single mutation (rtM204I). Virus with double mutations (rtL180M + rtM204V) were obtained from one, zero, and one patients, respectively. Two samples were wild-type virus and may have resulted from the patients (one each from the lamivudine and combination groups) having a 'drug holiday' [513844], [513846].

Some exploratory analyses were reported; by grouping all patients by serum HBV DNA level at week 24 [513844]. Those with the lowest HBV levels were more likely to become HBeAg-negative, have undetectable HBV, have ALT normalization, and less likely to have virus breakthrough by week 52.

The major conclusions from this trial were that telbivudine had a greater antiviral effect than lamivudine and that the combination of telbivudine with lamivudine showed no

advantage over telbivudine alone; the combination was not better than telbivudine monotherapy for any endpoint. All treatments were well tolerated and no safety issues were identified. It may be expected that telbivudine, achieving a greater degree of viral suppression, may allow less opportunity for the selection of resistant virus than with lamivudine; the results, although preliminary, and with very small patient numbers, possibly support this expectation. For phase III trials, telbivudine will be evaluated with the 600-mg dose [513844].

Valtorcitabine was due to commence IIb trials in 2003. It is expected to be tested in combination with telbivudine [513826] in 2004 and, if the combination is successful, phase III trials of the combination may start in 2005.

Phase III

Phase III trials of telbivudine are underway [513833]. The program is to include 1200 patients from approximately 120 clinical research sites in Asia, Europe and North America and will evaluate the safety and efficacy of telbivudine compared with standard treatment in patients with HBeAg-positive and HBeAg-negative compensated liver disease [475756].

Side Effects and Contraindications

There have been no identified safety issues arising from the phase I/II or phase IIb trials of telbivudine. The adverse events recorded have been similar to those of lamivudine which has a good safety record [513850]. Following 24 weeks of treatment, there were no serious treatment-related adverse events, no discontinuations for adverse events and no dose-related adverse events or laboratory abnormalities [513850]. At 52 weeks, there were no identified safety issues [513846] although one patient with creatine phosphokinase elevation had treatment interrupted [513844].

Torcitabine, as its di-valinyl ester prodrug, has been evaluated only at low doses (400 mg prodrug is equivalent to approximately 170 mg active drug) in a single phase I/II trial, but so far it was well tolerated [513826]. There are no data available for the mono-valinyl ester, now known as valtorcitabine, which is the prodrug selected for the development of torcitabine.

Patent commentary

WO-00009531 claims methods for the treatment of hepatitis B viral infection comprising the use of 2'-deoxy-β-L-erythro-pentofurano-nucleoside derivatives or prodrugs thereof, either alone or in combination with other anti-HBV agents, and pharmaceutical compositions comprising them.

WO-00196353 claims novel 3'-ester prodrugs of β-L-nucleoside derivatives, and their salts, pharmaceutical compositions comprising them, and their use in the treatment of hepatitis B virus infection, either alone or in combination with other anti-hepatitis B agents. The 3',5'-di-O-L-valine ester of 2'-deoxy-β-L-cytidine is one of two compounds specifically claimed.

Current Opinion

In my personal opinion, only rarely is a compound, such as telbivudine, discovered to have such good clinical activity

together with such an excellent toxicological evaluation (all the tests completed so far have shown negative results). Thus, it is likely to have good prospects for becoming an approved and generally accepted treatment for HBV. But how is it to be used? Viral resistance studies have shown that telbivudine should not be used to treat patients failing on lamivudine therapy. The 52-week phase IIb trial, now continuing as a follow-on study, showed that monotherapy with telbivudine gave a better suppression of HBV and better ALT normalization than with lamivudine. The combination gave no advantage in any endpoint over telbivudine monotherapy. The continuing study may show whether the appearance of viral resistance is delayed by telbivudine compared with lamivudine. So far, the trend favors telbivudine. Perhaps telbivudine will be used instead of lamivudine.

In comparison with other drugs both in clinical use and in development, telbivudine appears to be the most effective at reducing HBV DNA levels. However, clevudine showed prolonged effect in preventing virus rebound to pretreatment levels after stopping therapy. In a phase I/II trial, at a daily dose of 100 mg, HBV DNA levels were reduced by 2.95 log at the end of 4 weeks of therapy, and were still 2.7 log below baseline at 6 months [464238]. However, until an antiviral mechanism has been elucidated for this prolonged effect, one is not sure if this is a great benefit or a warning sign. If it is the former, then combining telbivudine with clevudine could be a good option. The latter is suggested, perhaps, by the withdrawal of support by Gilead for the development of this product [494552]. Combination of telbivudine with entecavir may be a better option. Entecavir is undergoing phase III trials in nucleoside-naïve and lamivudine-resistant patients [482521], [482527]. There may be a similar lack of cross-resistance between telbivudine (an L-nucleoside, like lamivudine) and entecavir.

Perhaps combination with famciclovir should be considered. Although famciclovir, the oral prodrug of penciclovir, is widely available for the treatment of herpes virus infections, its development for HBV infections was terminated due to the high doses (and high cost) needed to treat HBV. However, Korba [513849] demonstrated that there was

considerable synergy when lamivudine and penciclovir were combined. In cell culture using the 2.2.15 cell line, the IC_{50} value of the combination was approximately 20-fold less than that with either agent alone. Synergy was also demonstrated in the woodchuck model. If similar results were to be found with telbivudine combined with penciclovir, then there would be the prospect of using each compound at a slightly reduced dose (to keep the cost reasonable), while still obtaining enhanced HBV suppression. As the risk of viral breakthrough seems to be minimized by greater HBV suppression, this may be a good option to try.

Combination with valtorcitabine looks promising. As telbivudine preferentially inhibits the second strand of HBV DNA synthesis whereas torcitabine inhibits both the first and second strand of HBV DNA synthesis, the genetic barrier will be increased; the virus would have to overcome the inhibition of two steps in its replication cycle and two drugs inhibiting one of those steps. This combination gave good results in the woodchuck model. Early results from a phase I/II trial with val-L-dC indicate that torcitabine (equivalent dose 170 mg) was less effective than telbivudine at 25 mg. Safety is another important factor to consider. Torcitabine preclinical toxicity testing has shown only minor effects so far, but these were more than with telbivudine. Therefore, I do not see a place for monotherapy with valtorcitabine. However, combination with telbivudine gives synergy which is optimal at a 1:1 ratio, but remains similar at a 3:1 ratio of telbivudine:torcitabine. This gives some flexibility in the choice of ratio which may be chosen not just on efficacy considerations, but also on safety grounds. Current plans for the clinical development of valtorcitabine focuses on combination therapy [513833].

The development of L-dA is not being progressed at present. If it was found to be active against clinical strains of HBV resistant to telbivudine and torcitabine, then that would give a rationale for its progression.

Acknowledgements

The author acknowledges Dr Richard Boehme (Idenix Pharmaceuticals Inc) for kindly providing copies of slides and posters presented at a number of conferences.

Licensing

Novartis Pharma AG

In March 2003, Novartis signed an agreement whereby it paid Idenix a US \$75 million license fee for rights to telbivudine and valtorcitabine [489012]. In May 2003, the agreement was changed so that Novartis would cover all global clinical development costs, and Idenix and Novartis would co-promote the products in the US and Europe. Throughout the rest of the world, Novartis would commercialize the products and make royalty-based payments to Idenix [489012].

Sumitomo Pharmaceuticals Co Ltd

In June 2001, Novirio entered into an agreement with Sumitomo Pharmaceuticals Co Ltd for the commercialization of L-dT for the treatment of hepatitis B infection. Under the terms of the agreement, Sumitomo was to co-develop and market L-dT in Japan, South Korea, Taiwan and China, in exchange for up front and milestone payments in the aggregate amount of US \$46 million. Global development costs plus royalties on the sale of the product in the agreed territories would be shared. Novirio retained all development and commercial rights to L-dT for the rest of the world and intended to build its own sales and marketing infrastructure in North America and Europe to support the commercialization of L-dT and subsequent Novirio product launches [414197].

Development history

As of August 2002, phase III trials of telbivudine were underway in the US [462525]. In 2003, Idenix and Novartis expected patient enrollment to be completed in the first quarter of 2004 and an NDA submission in the fourth quarter of 2005 [476555], [491099], [513950]. By January 2002, telbivudine was also undergoing a phase IIa trial in combination with val-L-dC [437041] and by September 2002, a phase IIb trial of telbivudine in combination with lamivudine was underway [463285].

By May 2001, torcitabine, as its divaliny ester, was undergoing phase I/II trials [408263], and was expected to enter phase III trials in 2003 [435762]. In May 2003, Novartis anticipated that launch would not be before 2006 [491099].

Telbivudine

Developer	Country	Status	Indication	Date	Reference
Idenix Pharmaceuticals Inc	US	Phase III	Hepatitis B virus infection	22-AUG-02	462525
Novartis Pharma AG	US	Phase III	Hepatitis B virus infection	26-MAR-03	483669
Idenix Pharmaceuticals Inc	South East Asia	Discovery	Hepatitis B virus infection	01-JUL-01	414197
Novartis Pharma AG	South East Asia	Discovery	Hepatitis B virus infection	26-MAR-03	483669
Sumitomo Pharmaceuticals Co Ltd	South East Asia	Discovery	Hepatitis B virus infection	01-JUL-01	414197

Torcitabine (as prodrug)

Developer	Country	Status	Indication	Date	Reference
Idenix Pharmaceuticals Inc	US	Phase II	Hepatitis B virus infection	07-MAY-01	408263
Novartis Pharma AG	US	Phase II	Hepatitis B virus infection	26-MAR-03	483669

Literature classifications

Chemistry

Study Type	Result	Reference
Synthesis of telbivudine	A six-step synthesis yielding 20 g of telbivudine was developed. Currently, unpublished large-scale syntheses are used.	364588 513833
Synthesis of torcitabine	A seven-step synthesis yielding 20 g of torcitabine was developed. Currently, unpublished large-scale syntheses are used for the prodrug, valtorcitabine.	364588 513833
Synthesis of L-dA	A six-step synthesis yielding 20 g of L-dA was developed.	364575
SAR with prodrugs of torcitabine	Prodrugs were assessed in monkeys; monovaline gave the best result but the divaline was chosen due to simpler synthesis. A phase III trial was interrupted because the monoval ester was found to be less hygroscopic and more stable. In the fourth quarter of 2002, 3-valinyl-L-dC was used in the continuation of phase III trials.	405816
SAR with telbivudine, torcitabine and L-dA	All three were active against HBV. EC ₅₀ values for telbivudine and torcitabine were 0.2 and 2 μM, respectively, for L-dA in the HepG 2.2.15 cell culture assay. Their activity was highly specific, being inactive against HIV-1, herpes simplex virus (HSV)-1, HSV-2, varicella-zoster virus, Epstein-Barr virus, human cytomegalovirus, adenovirus, influenza A and B, measles virus, parainfluenza, rhinovirus and respiratory syncytial virus at concentrations over 100 μM. Other L-nucleosides were either less active or less specific for HBV.	397171 460857

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vitro</i>	Selectivity of telbivudine, torcitabine and L-dA	Inhibition of human polymerases α, β and γ by 5-triphosphate	Inactive at 100 μM	397171
<i>In vitro</i>	Cytotoxicity of telbivudine, torcitabine and L-dA	Human hepatoma cells, human foreskin cells, primary human peripheral blood monocyte cells	50% cytotoxic concentration ~1000 μM	397171
<i>In vitro</i>	Cytotoxicity of telbivudine, torcitabine and L-dA	Human bone marrow stem cells in primary culture	No effect on granulocyte-macrophage colony-forming unit or erythroid burst-forming unit precursors at 50 μM	397171 462643

Biology (continued)

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vitro</i>	Mechanism of action of telbivudine, forcitabine and L-dA	Inhibition of WHBV polymerase	L-81TP, IC ₅₀ = 0.24 μM; L-dGTP and L-dUTP, IC ₅₀ = 1.8 and 5.3 μM, respectively. The IC ₅₀ value of L-dATP was approximately 1 μM.	397171 458973
<i>In vitro</i>	Mechanism of action of telbivudine and forcitabine	Information not given	Telbivudine preferentially inhibits the second strand of HBV DNA synthesis whereas forcitabine inhibits both first and second strands of HBV DNA synthesis.	513826
<i>In vitro</i>	Antiviral effect and synergy of telbivudine and forcitabine	HepG2/2.15 cells	EC ₅₀ values = 1.2 and 1.1 μM for telbivudine and forcitabine, respectively. When combined at a ratio of 1:1, 3:1 and 3:1 the respective EC ₅₀ values were 0.30, 0.33 and 0.41 μM.	513625
<i>In vivo</i>	Antiviral effect of telbivudine, val-L-dC or lamivudine	Woodchucks (chronically infected, n = 5/group) treated for 12 weeks with telbivudine or val-L-dC (10 mg/kg once daily) or lamivudine (15 mg/kg once daily). Reduction in viral DNA (log ₁₀ copies/ml) measured (>10 is to the limit of detection, 30 copies/ml)	With telbivudine alone, reduction in viral DNA was at 4 weeks, 5 to 7 log ₁₀ in 4/5 animals and >10 log ₁₀ in 1/5 animals; at 12 to 14 weeks, >10 log ₁₀ in 5/5 animals. With val-L-dC alone, reduction was at 4 weeks, 5 to 7 log ₁₀ in 4/5 animals, >10 log ₁₀ in 0/5 animals; at 12 to 14 weeks, 7 to 8 log ₁₀ in 3/5 animals, >10 log ₁₀ in 2/5 animals. With lamivudine alone at 4 weeks, 5 log ₁₀ in 2/5 animals, 2 to 4 log ₁₀ in 3/5 animals; at 12 weeks, 1 to 2 log ₁₀ in 2/5 animals, 1 to 5 log ₁₀ in 3/5 animals.	435422 513625
<i>In vivo</i>	Antiviral effect of telbivudine and val-L-dC combination	Woodchucks (chronically infected, n = 5/group) treated for 12 weeks with telbivudine and val-L-dC (each at 10 mg/kg once daily). Reduction in viral DNA (log ₁₀ copies/ml) measured (>10 is to the limit of detection, 30 copies/ml)	Reduction of viral DNA with telbivudine and val-L-dC combined was at 4 weeks, 5 to 7 log ₁₀ in 1/5 animals, >10 log ₁₀ in 4/5 animals; at 12 weeks, >10 log ₁₀ in 5/5 animals.	435422 513625
<i>In vivo</i>	Antiviral effect of telbivudine and lamivudine combination	Woodchucks (chronically infected, n = 5/group) treated for 12 weeks with telbivudine (10 mg/kg once daily) and lamivudine (15 mg/kg once daily). Reduction in viral DNA (log ₁₀ copies/ml) measured (>10 is to the limit of detection, 30 copies/ml)	Reduction of viral DNA with telbivudine and lamivudine combined was at 4 weeks, 6 to 7 log ₁₀ in 5/5 animals, >10 log ₁₀ in 0/5 animals; at 12 weeks, 7 to 8 log ₁₀ in 2/5 animals, >10 log ₁₀ in 3/5 animals.	435422 513625
<i>In vivo</i>	Antiviral effect of L-dA	Woodchucks (chronically infected) treated for 4 weeks with L-dA (10 mg/kg once daily). Reduction in viral DNA (log ₁₀ copies/ml) determined	At 4 weeks, there was a 1 to 2 log ₁₀ reduction.	397171

Metabolism

Study Type	Effect Studied	Model Used	Result	Reference
<i>In vivo</i>	Pharmacokinetics of telbivudine and forcitabine	Cynomolgus monkeys	For telbivudine, the T _{1/2α} was 1 to 4 h, T _{1/2β} was approximately 1.5 h and bioavailability was 69%. This compared with a bioavailability of 16% for forcitabine.	460857

Metabolism (continued)

Study Type	Effect Studied	Model Used	Result	Reference
<i>In vivo</i>	Pharmacokinetics of torcitabine from 3'-5'-di-O-valinyl-L-dC.	Cynomolgus monkeys	Bioavailability was at least 65%.	460857
<i>In vivo</i>	Pharmacokinetics of torcitabine from valtoritabine.	Cynomolgus monkeys	Bioavailability at 84% was improved over that from the divalanyl ester.	513833
<i>In vitro</i>	Formation of triphosphate derivatives of telbivudine and torcitabine.	HepG2 cells and primary human hepatocytes incubated with 10 μ M of nucleoside for 24 h.	The intracellular concentration of L-dTTP was 28 and 17 pmol/10 ⁶ cells for telbivudine and torcitabine, respectively. Phosphorylation was unchanged in the presence of torcitabine. The intracellular concentration of L-dCTP was 72 and 90 pmol/10 ⁶ cells, respectively. L-dUTP was 18 and 44 pmol/10 ⁶ cells, respectively. Phosphorylation was unchanged in the presence of telbivudine.	458973
<i>In vitro</i>	Stability of triphosphate derivatives of telbivudine and torcitabine.	Intracellular concentrations of L-dTTP from telbivudine and L-dCTP (L-dUTP) from torcitabine in HepG2 cells, measured over a 24 h period after removal of drug from cell cultures.	The t _{1/2} of L-dTTP was at least 15 h. At 24 h, the concentration of L-dTTP was 7 pmol/10 ⁶ cells, well above the IC ₅₀ value (approximately 1 μ M) for HBV DNA polymerase, and just above the IC ₅₀ (approximately 5 μ M). The t _{1/2} of L-dCTP and L-dUTP were at least 15 h. At 24 h, the concentrations of L-dCTP and L-dUTP were 32 and 14 pmol/10 ⁶ cells, respectively.	458973 397170

Clinical

Study Type	Model Used	Result	Reference
Phase III trial of telbivudine	Randomized, placebo-controlled, dose-escalation trial of telbivudine (25 to 800 mg) administered once daily for 28 days with 32 weeks follow-up. (n = 7 patients/cohort including one on placebo)	All doses were active. HBV DNA reduction of 2.5 and 3.8 log ₁₀ for 25 and 800 mg, respectively. There was a trend towards slower telbivudine HBV DNA base levels with higher doses (with 800 mg, 2 and 1 log ₁₀ reductions at 8 and 16 weeks, respectively).	513850
Phase IIb trial of telbivudine and lamivudine each alone and in combination	Randomized, placebo-controlled trial of telbivudine (400 or 800 mg) alone or with lamivudine (100 mg) versus lamivudine alone, once daily dosing for 52 weeks (n = 20 patients/group); analysis at 12 and 24 weeks completed, preliminary results for the 52-week time point.	At 12 weeks, with lamivudine alone, HBV DNA reduction was nearly 5 log ₁₀ for all telbivudine groups; the reduction was between 5 and 6 log ₁₀ . At 24 weeks, there was little change with lamivudine (4.7 log ₁₀). Both telbivudine-only groups shared mean reductions of 6.1 log ₁₀ (combination groups = 6.2 log ₁₀). Both these were significantly better than lamivudine alone (p = 0.05 and 0.01, respectively). Patients negative for HBV DNA by PCR including the lamivudine group (16%), telbivudine groups (32%) and combination groups (32%). At 52 weeks, the reductions in HBV DNA levels were maintained; lamivudine (4.6 log ₁₀) mean for both telbivudine-only groups (6.0 log ₁₀) and combination (6.0 log ₁₀) (p < 0.05 for telbivudine groups versus lamivudine). The proportion of patients having undetectable HBV DNA by PCR was 32, 61 (p < 0.05 versus lamivudine) and 49%, respectively. Those with HBeAg loss (all but one patient seroconverted) were 28, 33 and 17%, respectively. ALT normalizations were similar in all groups (approximately 75% of patients) up to 24 weeks. By 52 weeks, the proportions were 63, 86 (p < 0.05 versus lamivudine) and 78%, respectively.	513856 513824 513846 513850
Phase I/II trial of val-L-dC	Randomized, placebo-controlled, dose-escalation trial of val-L-dC (50 to 1200 mg) once daily for 28 days with 12 weeks follow-up. (n = 7 patients/cohort including one on placebo)	HBV DNA reductions of 1 log ₁₀ for the 50 mg dose to 2 log ₁₀ for the 400 mg dose (equivalent to 170 mg L-dC) were observed. The decision was taken to switch to the methyl valine ester (valtoritabine) as prodrug.	519344

Associated patent for telbivudine

Title β -L-2'-deoxynucleosides for the treatment of hepatitis B.

Assignee Centre National de la Recherche Scientifique, Novirio Pharmaceuticals Limited

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Inventors Gosselin G, Imbach J-L, Bryant ML.

Associated patent for torcitabine

Title 3'-Ester prodrugs of 2-deoxy- β -L-nucleosides for the treatment of hepatitis B virus infection.

Assignee Novirio Pharmaceuticals Limited, Centre National de la Recherche Scientifique (CNRS)

Publication WO-00196353 20-DEC-01

Priority US-00212100 15-JUN-00

Inventors Bryant ML, Gosselin G, Imbach J-L.

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