Drugs of the Future 2001, 26(4): 364-374

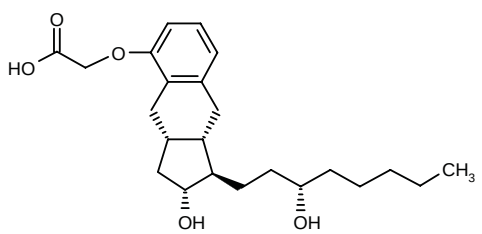
CCC: 0377-8282/2001

UT-15

Treatment of Pulmonary Hypertension
Treatment of Peripheral Vascular Disease

Uniprost
BW-15AU
LRX-15
U-62840
15AU81
Remodulin™

9-Deoxy-3,7-(1',3'-interphenylene)-2',9-methano-3-oxa-4,5,6-trinor-13,14-dihydroprostaglandin F_1
(1*R*,2*R*,3a*S*,9a*S*)-2-[2-Hydroxy-1-[3(*S*)-hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]inden-5-yloxy]acetic acid



$C_{23}H_{34}O_5$ Mol wt: 390.524

CAS: 081846-19-7

EN: 157437

Synthesis

UT-15 can be prepared by several related ways:

1) The reaction of the prostaglandin E_1 derivative (I) with *N*,*S*-dimethylphenylsulfonimide (II) by means of methylmagnesium chloride in THF gives intermediate (III), which is treated with aluminum amalgam in AcOH/water to yield the methylene derivative (IV). Hydroboration of (IV) with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF affords the hydroxymethyl derivative (V), which is treated with methanesulfonyl chloride and TEA in dichloromethane to provide mesylate (VI). Desilylation of compound (VI) with TBAF in THF gives the phenol derivative (VII), which is cyclized by means of NaH in THF yielding the tricyclic prostaglandin derivative (VIII). Alkylation of compound (VIII) with methyl bromoacetate (IX) by means of NaH in glyme affords the 2-hydroxyacetate derivative (X), which is treated first with AcOH/water in order to eliminate the THP protecting groups, and then with KOH in methanol/water to hydrolyze the methyl ester group providing the prostaglandin F_1 derivative (XI). Finally, this compound is hydrogenated over Pd/C in ethyl acetate (1-3). Scheme 1.

2) The reduction of 2-octyn-1-ol (XII) with bis(2-methoxyethoxy)aluminum hydride in toluene/THF gives 2-octen-1-ol (XIII), which is treated with *tert*-butyl hydroperoxide, (+)-diethyl L-tartrate and titanium tetraisopropoxide in dichloromethane yielding epoxide (XIV). The latter is reduced with bis(2-ethoxyethoxy)aluminum hydride in toluene/THF, affording the chiral diol (XV). The selective monotosylation of (XV) with TsCl in pyridine provides the primary tosylate (XVI), which is treated with NaI in hot acetone to furnish 1-iodo-3-octanol (XVII). Protection of (XVII) with dihydropyran and pyridine hydrochloride gives the tetrahydropyranyl ether (XVIII), which is condensed with dimethyl methylphosphonate (XIX) by means of BuLi and TEA in THF to yield the phosphonate (XX). Condensation of compound (XX) with 5-methoxy-2,3,3a,4-tetrahydronaphtho[2,3-*b*]furan-2-one (XXI) by means of BuLi in THF affords the tricyclic adduct (XXII), which is hydrogenated with H_2 over Pd/C in ethanol to provide compound (XXIII). Isomerization of (XXIII) with NaOH in refluxing ethanol gives diastereomer (XXIV). The reduction of the carbonyl group of (XXIV) with $NaBH_4$ in methanol, followed by deprotection with AcOH in THF yields compound (XXV). The demethylation of compound (XXV) by means of BuLi and Ph_2PH in THF affords the tricyclic phenol (XXVI), which is condensed with 2-chloroacetonitrile (XXVII) by means of K_2CO_3 in refluxing acetone to provide the precursor (XXVIII). Finally, the cyano group of (XXVIII) is hydrolyzed with KOH in refluxing water (4). Scheme 2.

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3) Reaction of 3-methoxybenzyl alcohol (XXIX) with TBDMS-Cl and imidazole in dichloromethane gives the silyl ether (XXX), which is condensed with allyl bromide (XXXI) by means of BuLi in hexane to yield the 2-allyl derivative (XXXII). Deprotection of (XXXII) by means of TBAF in THF affords the benzyl alcohol (XXXIII), which is oxidized with oxalyl chloride and TEA in DMSO/dichloromethane to provide 2-allyl-3-methoxybenzaldehyde (XXXIV). Condensation of compound (XXXIV) with the chiral 1-decyne (XXXV) by means of ethylmagnesium bromide in THF gives the secondary alcohol (XXXVI), which is oxidized with pyridinium chlorochromate (PCC) in dichloromethane yielding ketone (XXXVII). The enantioselective reduction of ketone (XXXVII) by means of trimethylboroxine (TMBO), BH_3/Me_2S and (*R*)-(2-pyrrolidinyl)diphenylmethanol in toluene affords the chiral secondary alcohol (XXXVIII) as a single diastereomer. Silylation of alcohol (XXXVIII) with TBDMS-Cl and imidazole yields the corresponding ether (XXXIX), which is submitted to cyclization catalyzed by $Co_2(CO)_8$ in refluxing acetonitrile affording the tricyclic ketone (XL). Hydrogenation of the conjugated double bond of (XL) with H_2 over Pd/C in ethanol provides the saturated ketone (XLI), which is reduced with $NaBH_4$ in ethanol to give the tricyclic alcohol (XLII). Elimination of the tetrahydropyranyl-protecting group of (XLII) with *p*-toluensulfonic acid in methanol provides diol (XXV) already described (5). Scheme 3.

Description

Crystals, m.p. 122-4 °C (4).

Introduction

Pulmonary hypertension is a relatively rare and serious progressive lung disease that was first described in 1891. It is characterized by increased blood pressure within the pulmonary arterial system above normal (25 mmHg at rest and > 30 mmHg during exercise *vs.* 14 mmHg at rest) and symptoms include fatigue, shortness of breath after minimal exertion, edema, dyspnea, dizziness and fainting. The high pulmonary blood pressure causes injury to the endothelial cells lining lung capillaries, thus affecting their interaction with nearby smooth muscle cells. The result is that smooth muscles contract more than normal, thus narrowing the vessels and increasing resistance to blood flow. This increase in resistance in turn places stress on the right ventricle and failure of this ventricle may develop due to the required increase in work. The disorder may be subdivided into 2 major subtypes: primary pulmonary hypertension (PPH) which is evident in the absence of any known cause, and secondary pulmonary hypertension (PH) which is the result of another underlying condition such as scleroderma, chronic obstructive pulmonary disease, systemic lupus erythematosus, HIV infection and portal hypertension. Persistent pulmonary hypertension of the newborn (PPHN) is another form of the disease that afflicts newborns (6).

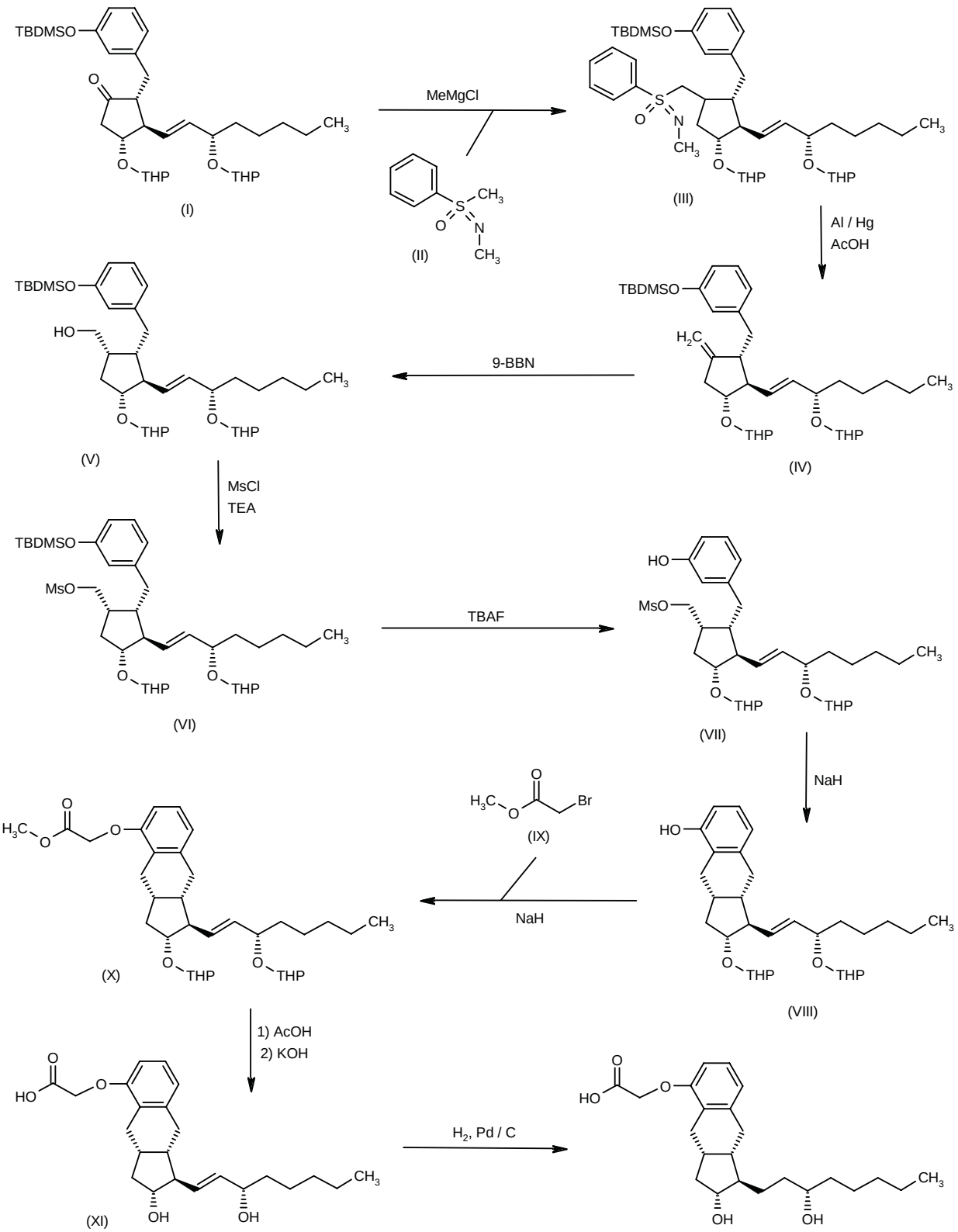
Until relatively recently, there was nothing available to treat patients diagnosed with PPH. However, with the discovery of pulmonary vasodilators, treatment outcome for PPH patients has significantly improved. At present treatment regimens reduce or facilitate the work of the right ventricle. Treatment can include anticoagulants which decrease the tendency to clot allowing blood to flow more freely, diuretics to reduce the amount of fluid in the body thus decreasing the cardiac workload and calcium channel blockers to relax cardiac smooth muscle.

Prostacyclin (prostaglandin I_2) is the most potent vasodilator affecting both the pulmonary and systemic circulations that also prevents clot formation (7). It is a prostaglandin (PG) found in all tissues and body fluids that is the major metabolite of arachidonic acid in the vasculature (8). Cyclooxygenase metabolism of arachidonic acid produces PGG_2 which is further metabolized by PG hydroperoxide to PGH_2. Both PGG_2 and PGH_2 are converted to prostacyclin by PGI_2 synthetase (9, 10). The majority of prostacyclin is produced by the endothelium and by smooth muscle (8, 9, 11, 12). Prostacyclin induces vasodilation by increasing intracellular cAMP of vascular smooth muscle and it has also been shown to inhibit platelet aggregation and adhesion (13-15). Prostacyclin has therefore been indicated for various cardiovascular diseases including PPH as well as congestive heart failure, myocardial ischemia, Raynaud's phenomenon and peripheral vascular disease.

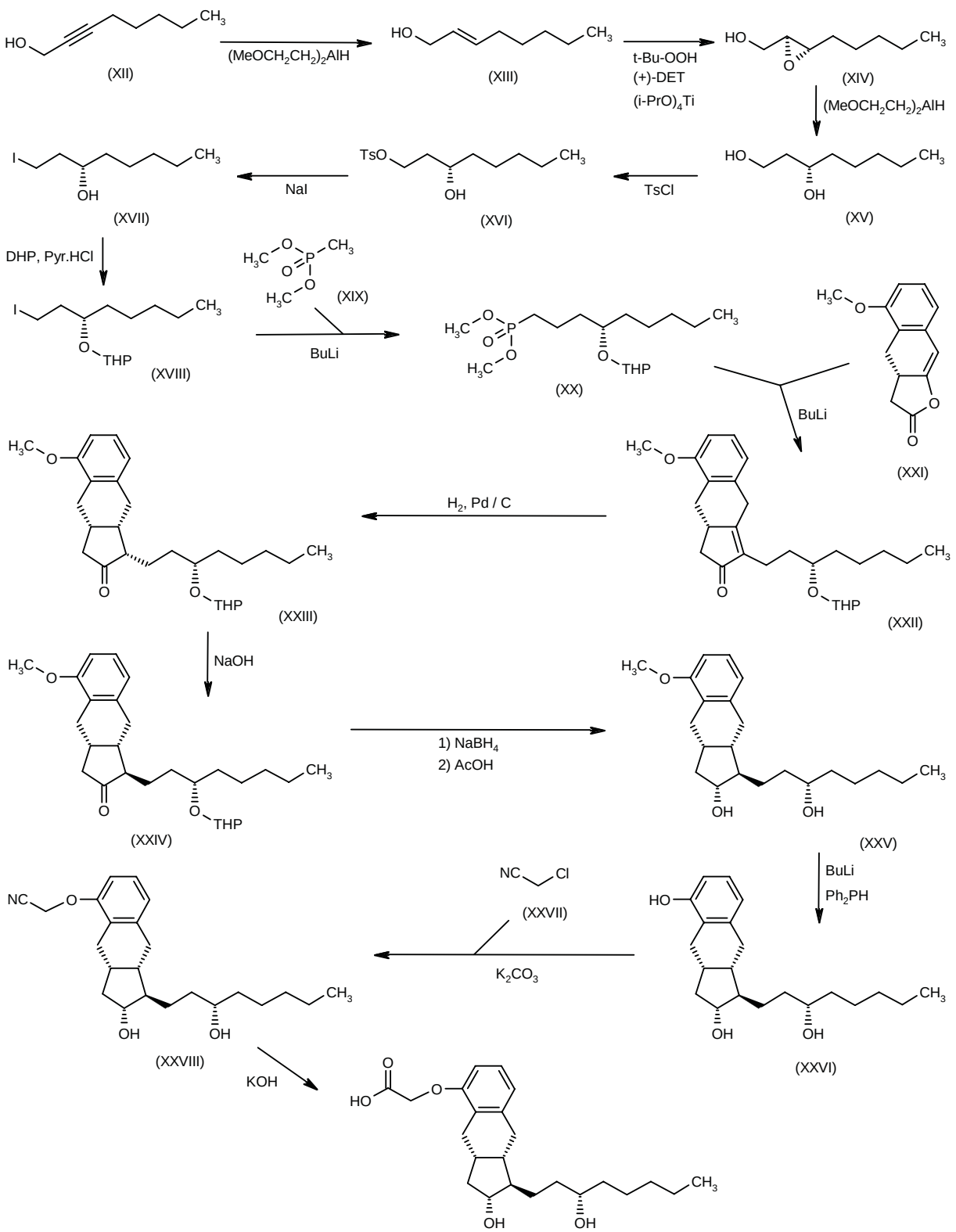
Although prostacyclin appears to be an ideal solution for a number of cardiovascular disorders, it has several disadvantages. Endogenous prostacyclin and its synthetic counterpart, epoprostenol, have extremely short half-lives of approximately 3-6 min and are degraded by the gastrointestinal tract. Thus clinically, the route of epoprostenol administration must be continuous i.v. infusion. The agent is infused via a catheter implanted in the neck with delivery controlled by a portable pump. Both prostacyclin and epoprostenol are also degraded by light and epoprostenol must be stored freeze dried at temperatures between 15 and 25 °C to be later reconstituted prior to administration in a glycine buffer of pH 10.5. Epoprostenol must be protected from light during reconstitution and during infusion and a single infusion should be completed within 8 h of reconstitution. Due to the uncomfortable and inefficient delivery and instability of the molecule, the search for new prostacyclin analogs was initiated. However, the search has proved difficult and only a few prostacyclin analogs, as shown in Table I, have displayed potential clinical efficacy (2).

Fortunately, 2 promising prostacyclin analogs have emerged. Beraprost is an oral derivative of prostacyclin in phase III trials that is chemically stable. Beraprost like prostacyclin is a vasodilator that also inhibits platelet aggregation and proliferation of smooth muscle cells. However, the agent may only be effective as a treatment for early-stage pulmonary hypertension or early-stage

Scheme 1: Synthesis of UT-15



Scheme 2: Synthesis of UT-15



Scheme 3: Synthesis of Intermediate (XXV) of UT-15

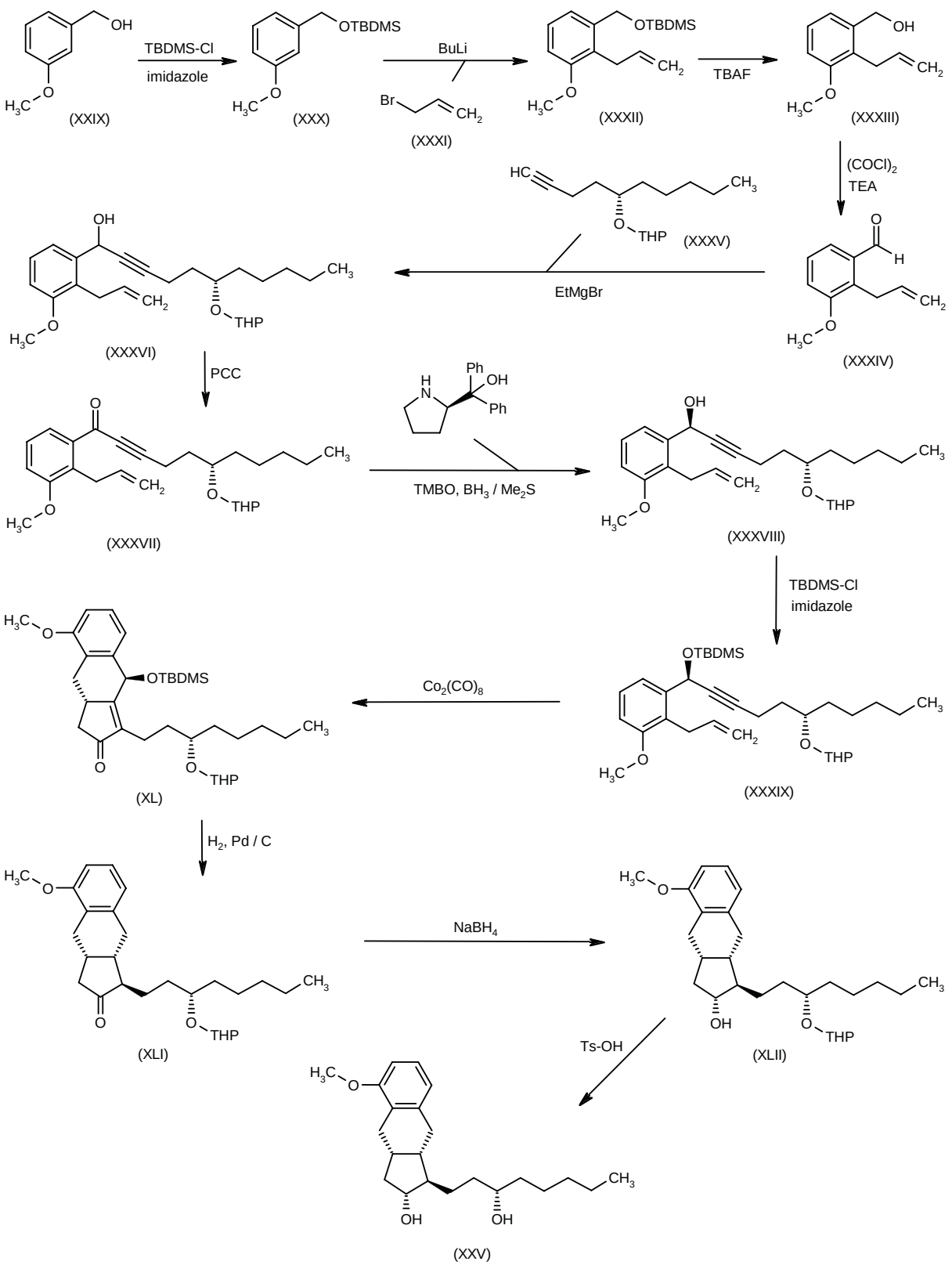
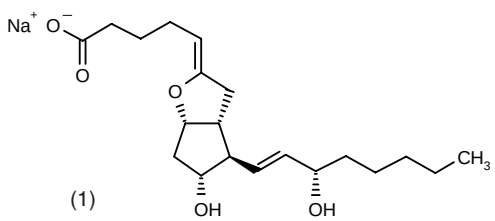
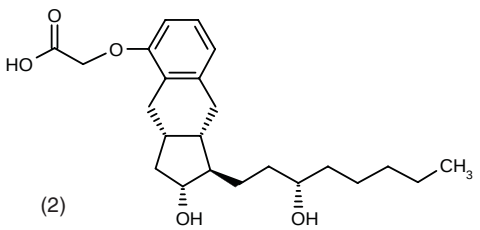


Table I: Prostacyclin analogs for the treatment of pulmonary hypertension [Prous Science Ensemble database].

Drug Name	Source	Route of Administration	Status
1. Epoprostenol sodium	GlaxoSmithKline	Continuous intravenous	Launched 1998*
2. UT-15 (Remodulin™)	United Therapeutics	Subcutaneous	Preregistered
3. Beraprost sodium	United Therapeutics	Oral	Phase III**
4. Iloprost	Schering AG	Inhalation or oral	Phase III**
5. AFP-07	Asahi Glass	Intravenous or oral	Preclinical



(1)



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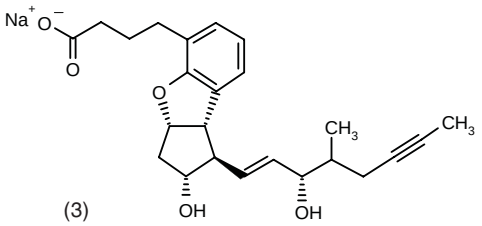

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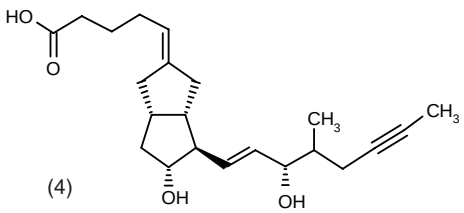

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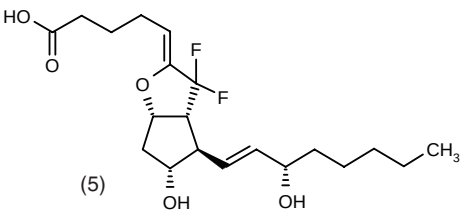

(5)

*Previously launched in 1982 as an anticoagulant. **Marketed for the treatment of peripheral vascular diseases.

peripheral vascular disease since doses of the agent do not provide the constant plasma levels required to treat advanced-stage pulmonary hypertension or late-stage peripheral vascular disease (16). UT-15 (Remodulin™), on the other hand, is a chemically stable benzindene analog of prostacyclin that has shown potent preclinical and clinical efficacy and may be a potential treatment for advanced pulmonary hypertension and late-stage vascular disease. The compound is stable at room temperature for up to 5 years and is delivered via s.c. infusion using a MiniMed microinfusion device, thus eliminating the risk of sepsis infection and hospitalization associated with catheters (17). UT-15 has been chosen for further development.

Pharmacological Studies

The antiproliferative effects of UT-15 were demonstrated and shown to be mediated through a cAMP-dependent pathway in an *in vitro* study using human pulmonary artery smooth muscle cells (HPASMC) stimulated with fetal bovine serum (10%). A 91.6 ± 2.1% reduction in proliferation was observed as well as a 60.5 ± 3.9% decrease in [^{3}H]-thymidine incorporation. The agent significantly increased intracellular cAMP by approximately 120-fold and these high levels were sustained even 72 h after exposure to the agent. The adenylyl cyclase inhibitor 2'5'-dideoxyadenosine (DDA) markedly inhibited UT-15-induced elevations in cAMP (by 94.2%) in addition to decreasing cell number (72%) and [^{3}H]-thymidine incorporation (51%). The UT-15-induced increases in cAMP were suggested to be mediated via the prostacyclin receptor since the agent could only increase cAMP in human embryonic kidney (HEK) cells transiently transfected with the human prostacyclin receptor (18).

The efficacy of UT-15 was also shown *in vivo* in a study using a chronic hypoxia (exposure to 10% O_2 in a normobaric chamber for 3 weeks)-induced pulmonary hypertension rat model. UT-15 (0.1, 1 and 10 μg/ml) or a 5 kD polyethylene glycol diacetate derivative of the agent (PEG-UT-15; 1 and 3 mg) were administered

intratracheally (i.t.) and compared to the effects of papaverine (500-1000 μg). UT-15 and PEG-UT-15 (3 mg) significantly and dose-dependently decreased Ppa (26-38 to 1.2-4.2 mmHg) which was sustained for 2-3 and 5 h, respectively. The initial reductions in Ppa were similar to those observed with papaverine (to 3-5 mmHg). No significant reductions were seen in animals treated with the vehicle or PEG alone (19).

Results from an *in vivo* study using anesthetized dogs demonstrated that UT-15 (0.1, 0.3, 1 or 3 μg/kg/min for 4 h) has the potential to be used in the management of chronic congestive heart failure. Infusion of the respective doses of the agent caused dose-dependent reductions of 10, 43, 55 and 68% in mean arterial blood pressure. In addition, decreases in total peripheral resistance (TPR) of 20, 32, 56 and 73%, respectively, were observed. However, the action of UT-15 on the pulmonary vascular bed was unstable and not dose-dependent. Effects were rapid with peak action noted within 5-10 min of infusion and rapid recovery observed with cessation of the infusion. Decreases in pulmonary artery blood pressure of 9, 23, 22 and 18%, respectively, and reductions in pulmonary vascular resistance (PVR) of 9, 33, 30 and 23%, respectively, were observed. UT-15 treatment also resulted in decreases in inotrophy and lusitrophy and increases in heart rate and plasma angiotensin II levels. The increases in plasma angiotensin II correlated with the decreases in mean arterial blood pressure (20).

UT-15 was found to have immunosuppressive effects both alone and in combination with ciclosporin. *In vitro* studies have shown that UT-15 (0.1-10 μg/ml) inhibited human peripheral lymphocytes stimulated with phytohemagglutinin (10 μg/ml) and anti-CD3 (10 μg/ml) in a dose-dependent manner and synergistic effects were observed when the agent was combined with ciclosporin. Moreover, when the agent (0.05 mg/kg/day s.c. for 7 days starting on day 0 of transplantation) was administered *in vivo* to rabbits with renal allografts alone or in combination with ciclosporin (20 mg/kg i.v. perioperatively on day 0), allograft survival was potentiated and renal injury due to high-dose ciclosporin was attenuated (21).

Results from another *in vivo* study in rats demonstrated that UT-15 (50 μg/kg/day s.c. continuously with an osmotic pump for 14 days) given alone or in combination with rapamycin (0.0075 mg/kg/day continuous i.v. infusion for 14 days) and ciclosporin (0.375 mg/kg/day continuous i.v. infusion for 14 days) enhanced the immunosuppressive effects of donor-specific hepatocytes (50 millions/kg from Brown Norway rats) to prolong cardiac allograft (Brown Norway hearts in Wistar Furth recipients) survival. UT-15 in combination with rapamycin + ciclosporin prolonged survival to 35.2 ± 5.2 days as compared to 11.4 ± 1.7 and 27.2 ± 1.9 days seen with UT-15 alone and rapamycin + ciclosporin alone, respectively; hepatocyte treatment on its own did not prolong survival of cardiac allografts as compared to controls (7.2 ± 0.8 days). UT-15 alone, however, did not prolong survival of small bowel allografts (Brown Norway in Lewis recipients) in animals also treated with hepatocytes (10 ± 1.0 *vs.* 10.2 ± 1.9 days in controls) nor did the agent enhance the prolongation of survival seen with rapamycin + ciclosporin (17 ± 1.9 *vs.* 21.2 ± 1.5 days) (22).

Pharmacokinetics

A study has reported the development and validation of a radioimmunoassay (RIA) for determination of UT-15. The assay using [^{3}H]-UT-15 and plasma samples from dogs has a limit of quantification of 1.6 ng/ml. The assay was used to determine the pharmacokinetics of the agent after administration of a 20 μg/kg i.v. or i.t. dose to dogs. The plasma $t_{1/2}$ value following i.v. dosing was 2.8 min while that following i.t. dosing was slower with a mean bioavailability of 46% obtained (23).

Further pharmacokinetics for UT-15 (0.1, 0.3, 1 or 3 μg/kg/min infusion for 4 h) were reported and correlated to pharmacodynamic effects in a study using anesthetized dogs. A biphasic decay was observed with an initial $t_{1/2}$ of about 2 min obtained and a terminal elimination $t_{1/2}$ of 20 min. Plasma concentrations of the agent were found to correlate with the onset of reductions in TPR and PVR. The decreases in these parameters were generally sustained throughout infusion. Hysteresis in TPR as compared to plasma UT-15 concentrations were observed at the end of infusion, possibly due to saturation of UT-15 concentrations or the presence of active metabolites at the effect site and/or a delay in UT-15 clearance from the effect site as opposed to clearance from plasma. The maximum reductions in TPR and PVR in dogs that could be seen with the agent were estimated to be 66% (estimated EC_{50} = 8.6 ng/ml) and 22% (estimated EC_{50} = 11.3 ng/ml), respectively. These data suggest that although the extent of UT-15 action may be different, the agent showed no selectivity for pulmonary or peripheral circulation (24).

Clinical Studies

The efficacy of UT-15 as a treatment for congestive heart failure and pulmonary hypertension has been demonstrated clinically. The safety and efficacy of short-term infusion of UT-15 (starting at 10 ng/kg/min via a positive pressure infusion pump with 10 ng/kg/min escalations every 15 min until development of unacceptable adverse effects, and followed by a 90-min maintenance infusion at individual maximum tolerated doses [MTDs]) were evaluated in a multicenter, open-label, dose-escalation study in 12 patients with severe congestive heart failure (NYHA class III or IV). The mean MTD was 36 ± 15 ng/kg/min. Dose-limiting adverse events seen included headache (8 cases), restlessness (4), nausea (3), hypotension (2), flushing (2), jaw pain (1), sweating (1), dyspnea (1), pulmonary hypertension (1) and chest pain (1). Infusion of the agent until the MTD resulted in a significant decrease in systemic vascular resistance (1935 ± 774 *vs.* 1243 ± 351 dynes.s.cm^{-5}) and PVR

Box 1: Acute hemodynamic effects of UT-15 in severe congestive heart failure (25) [Prous Science CSline database].

Design	Open, placebo-controlled, multicenter clinical study
Population	Patients with severe congestive heart failure (n = 12)
Treatments	Placebo → UT-15 [dose titrated from 10 ng/kg/min i.v. infusion until dose-limiting side effects] → maximum tolerated dose i.v. infusion over 90 min
Adverse events	Adverse events UT at dose-limiting dose: headache 8/12 (66.7%), restlessness 4/12 (33.3%), nausea 3/12 (25%) UT at maintenance dose: abdominal/back/leg/pelvic pain 5/12 (41.7%), headache 3/12 (25%), restlessness 4/12 (33.3%), flushing 2/12 (16.7%)
Results	Systolic blood pressure (mmHg), change @ 90 min of maintenance dose: UT (-6) > P (4) Diastolic blood pressure (mmHg), change @ 90 min of maintenance dose: UT (-6) > P (5) Heart rate (bpm), change @ 90 min of maintenance dose: UT (6) ≥ P (3) Systemic vascular resistance (dyne·s/cm^5), change @ 90 min of maintenance dose: UT (-697) > P (59) Transpulmonary gradient (mmHg), change @ 90 min of maintenance dose: UT (-697) > P (0) Cardiac index (l/min/cm^2), change @ 90 min of maintenance dose: UT (0.9) > P (0)
Conclusions	UT-15 administration was associated with significant acute hemodynamic improvement in patients with congestive heart failure

Box 2: Efficacy and safety of UT-15 for primary pulmonary hypertension (26) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, multicenter clinical study
Population	Patients with primary pulmonary arterial hypertension, with NYHA class III/IV (n = 26)
Treatments	UT-15, dose titrated from 2.5 ng/kg/min [according to symptom control and adverse events] s.c. x 8 wks UT-15, dose titrated from 5 ng/kg/min [according to symptom control and adverse events] s.c. x 8 wks Placebo
Withdrawals	Intolerance/adverse events 2/26 (7.7%)
Adverse events	Headache 76%, diarrhea 59%, nausea/vomiting 59%, flushing 47%, jaw pain 35%
Results	6-min Walking distance (m), change @ 1 y: UT (28) > P (–6) Pulmonary vascular resistance index (U/m^2), change @ 1 y: P (–5) > UT (3)
Conclusions	UT-15 administered over 1 year was safe and improved hemodynamics and exercise tolerance in patients with primary pulmonary arterial hypertension

(395 ± 335 *vs.* 223 ± 198 dynes.s.cm^{-5}). A significant increase in the cardiac index (1.9 ± 0.7 *vs.* 2.6 ± 0.6 l/min/m^2) and a trend toward a mild decrease in pulmonary artery wedge pressure (18 ± 7 *vs.* 17 ± 6; $P = 0.055$) was also seen during dose escalation in 8 patients. Hemodynamic alterations were sustained throughout maintenance infusions and disappeared during washout (25) (Box 1).

The efficacy and safety of UT-15 (starting at 2.5 or 5 ng/kg/min) were demonstrated in a multicenter, double-blind, placebo-controlled, 2:1 randomized, 8-week trial involving 26 patients with PPH (NYHA class III/IV). The mean infusion rate for UT-15 was 14.5 ± 2.6 ng/kg/min. The most common adverse events included headache (76%), diarrhea (59%), nausea/vomiting (59%), flushing (47%) and jaw pain (35%); 2 patients discontinued due to intolerable adverse events. Pain and erythema at injection site were reported by 88 and 94% of the patients receiving UT-15, respectively, and 1 patient given placebo. Treatment was found to decrease PVR (–5 ± 1 *vs.* +3 ± 2 units in placebo) and increase 6-min walk distances (+28 ± 11 *vs.* –6 ± 27 m) (26) (Box 2).

Two studies conducted in 14 and 10 patients with PPH, respectively, showed the long-term efficacy and safety of chronic treatment with UT-15 (s.c.). In the first study, patients were treated for a mean of 13 ± 0.5 months. Six patients withdrew due to inability to achieve a tolerable dose based on available doses and limitation of infusion pump (1 patient), intolerable pain at infusion site (2 patients) and clinical deterioration (3 patients). Significant improvements in exercise endurance (6-min walk distances; 510 ± 49 *vs.* 430 ± 37 m at baseline) and improvements in NYHA functional class (2.4 ± 0.2 *vs.* 3 ± 0 at baseline) were observed in 7 of the 8 remaining patients. Treatment did not significantly affect mean pulmonary arterial pressure, cardiac index or PVR index (27) (Box 3).

In the second study, patients were treated for 11.8 ± 2.8 months and only 3 patients withdrew from this study, 1 each due to intolerable pain at injection site, failure to

Box 3: Efficacy of long-term s.c. infusion of UT-15 in primary pulmonary hypertension (27) [Prous Science CSline database].

Design	Open clinical study
Population	Patients with primary pulmonary arterial hypertension (n = 14)
Treatments	UT-15 s.c. x 1 y
Withdrawals	6/14 (42.8%) [adverse events 2/14 (14.3%), clinical deterioration 3/14 (21.4%), pump failure 1/14 (7.1%)]
Results	6-min Walking distance (m), change @ 1 y: 80 [$p = 0.04$ *vs.* baseline] Pulmonary arterial pressure (mmHg), change @ 1 y: 2 Cardiac output (l/min/m^2), change @ 1 y: 0.4 Pulmonary vascular resistance index (U/m^2), change @ 1 y: -2 NYHA classification, change @ 1 y: –0.6
Conclusions	1-year therapy with UT-15 improved exercise capacity in patients with primary pulmonary arterial hypertension

Box 4: Long-term effects of UT-15 on hemodynamics and exercise tolerance in primary pulmonary hypertension (28) [Prous Science CSline database]

Design	Open clinical study
Population	Patients with primary pulmonary arterial hypertension (n = 10)
Treatments	UT-15, s.c. x 1 y
Withdrawals	3/10 (30%) [adverse events 1/10 (10%), lost to follow-up 1/10 (10%), clinical deterioration 1/10 (10%)]
Results	6-min Walking distance (m), change @ 1 y: 64 [$p = 0.01$ *vs.* baseline] Pulmonary arterial pressure (mmHg), change @ 1 y: –3 Cardiac output (l/min), change @ 1 y: 0.78 [$p = 0.036$ *vs.* baseline] Pulmonary vascular resistance index (Wood units), change @ 1 y: –3.6 [$p = 0.045$ *vs.* baseline]
Conclusions	1-year therapy with UT-15 improved hemodynamics and exercise tolerance in patients with primary pulmonary arterial hypertension

Box 5: Efficacy and safety of chronic s.c. infusion of UT-15 in pulmonary arterial hypertension (29) [Prous Science CSline database].

Design	Randomized, placebo-controlled clinical study
Population	Patients with pulmonary arterial hypertension (n = 470)
Treatments	UT-15, s.c. x 12 wks Placebo, s.c. x 12 wks
Withdrawals	UT: adverse events 8%
Results	6-min Walking distance (m), change @ wk 12: P (–22) > UT (–2) [$p = 0.006$] Pulmonary arterial pressure (mmHg), change @ wk 12: UT (–3) > P (0) [$p < 0.0002$] Cardiac index (l/min/m^2), change @ wk 12: UT (0.2) > P (0) [$p < 0.0002$] Pulmonary vascular resistance index (U·m^2), change @ wk 12: UT (–4) > P (1) [$p < 0.0002$]
Conclusions	Chronic therapy with UT-15 was well tolerated and showed favorable hemodynamic effects in patients with pulmonary arterial hypertension

return at follow-up and clinical deterioration. A 22% improvement in cardiac output (4.36 ± 0.56 *vs.* 3.58 ± 0.43 l/min at baseline), a 24% significant decrease in PVR (11.4 ± 1.7 *vs.* 15 ± 1.8 units at baseline), a decrease in mean pulmonary arterial pressure (55 ± 5 *vs.* 58 ± 5 mmHg at baseline) and an improvement in NYHA functional class were observed in the remaining patients. In addition, 6-min walk distance was significantly improved (463 ± 35 *vs.* 399 ± 35 m at baseline) (28) (Box 4).

These results showing the efficacy and safety of chronic s.c. infusion of UT-15 were further corroborated in a large parallel, randomized, placebo-controlled, 12-week trial conducted in 470 patients with PPH. Within this study population, 271 patients had PPH, 90 had associated connective tissue disorders and 109 had associated congenital heart defects. Only 8% of the patients discontinued due to adverse events, and serious adverse events related to UT-15 treatment were seen in 6 patients.

Exercise capacity (6-min walk) was significantly increased in patients treated with UT-15 as compared to placebo (325 ± 8 *vs.* 305 ± 8 m). Treatment with the agent also significantly improved hemodynamic parameters (mean pulmonary arterial pressure: 59 ± 1 *vs.* 60 ± 1 mmHg; PVR index: 22 ± 1 *vs.* 26 ± 1 units.m^2; cardiac index: 2.6 ± 0.1 *vs.* 2.3 ± 0.1 l/m/m^2) and these effects were accompanied by improvements in clinical signs and symptoms (29) (Box 5).

Results from a phase II, dose escalation trial with a placebo run-in period conducted in 8 patients with severe, stable intermittent claudication (Fontaine classes IIb-III) demonstrated the safety and efficacy of UT-15 (starting at 10 ng/kg/min i.v. infusion with dose doubling every 60 min until development of unacceptable adverse events, and followed by a 2-h maintenance infusion at the MTD). No serious adverse events were related to UT-15 infusion. The most common adverse events included headache and nausea. The optimal infusion rate was determined to be 10-20 ng/kg/min. Ultrasonagraphic assessment of hemodynamic responses in lower limbs revealed that treatment significantly increased blood flow in the common femoral artery by 29% by the end of the maintenance infusion; levels were significantly sustained above baseline throughout the washout period. In addition, lower limb blood velocity was significantly increased in the common femoral artery and anterior tibial artery; blood velocity of the popliteal artery tended to be increased ($p = 0.062$). Arterial blood flow at the ankle that was undetectable prior to treatment in 2 patients became measurable during the maintenance infusion. Although there was no alteration in the ankle/brachial index, treatment significantly improved pulse volume (30).

United Therapeutics has filed an NDA with the FDA and a marketing authorization application (MAA) in France for approval of UT-15 for the treatment of pulmonary arterial hypertension (31).

Manufacturer

United Therapeutics Corp. (US).

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