Horizon Scanning Brief Report

Drug for bronchopulmonary dysplasia (BPD) of preterm infant 'PNEUMOSTEM®'

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NECA National Evidence-based Healthcare Collaborating Agency
H-SIGHT Horizon Scanning Service for Innovative Global Health Technology

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Basic information	
Identification No.	H-SIGHT-2015-299
Report No.	H-SIGHT-2015-003
Technology type	Drug
Name of technology	Allogeneic human Umbilical Cord Blood (hUCB)-drived mesenchymal stem cell (MSC)
Product and developer	PNEUMOSTEM® /Medipost Co., Ltd.
Target group	Pre-term infants at high risk for bronchopulmonary dysplasia (BPD) - 23 ~ 29th week of pregnancy - Body weight in birth 500 ~ 1,250 g - Continuous therapy with ventilator within 5 ~ 14 days after birth
Purpose	Although the BPD is one of major causes of death and complication of preterm infants, there is no distinct therapeutic method. Thus it was developed to prevent and treat BPD
Innovativeness	The first drug for BPD of preterm infants
Estimated time point of market entry in South Korea	Unpredictable /over 5 years/ 3-5 years /1~3 years/ within 1 year/ market entry
Stage of development	Health technology at research phase (pilot or Phase Ⅱ)
Current status of use (domestic and foreign)	• Foreign: Assigned as an 'orphan drug' by U.S. FDA (2013.12) Obtained approval for clinical study in U.S. (2014.9) Administered to 4 of total 12 subjects at Phase I and Phase II in U.S. (2015.3) Assigned as an 'orphan drug' by EU EMA (2015.7) • Domestic: Obtained patent (application no.: 10-2007-0010191) (2008) Assigned as an 'orphan drug at development phase' by EU EMA (2014) • Subject to total 70 infants in Samsung Seoul Hospital and Seoul Asan Hospital, phase II clinical study has been performed and administration to all the subjects was completed recently. It is scheduled to obverse efficacy of the drug for 6 months until October, 2015, perform confirmation and analysis of clinical data, and then submit a report of clinical study to the ministry of food and drug safety in the first half of 2016.
Technology setting	General hospital

Summary

Although the bronchopulmonary dysplasia (BPD) is one of main causes for death and complications of preterm infants, there is no distinct therapy up to now. The 'PNEUMOSTEM®' is a drug produced from mesenchymal stem cells extracted from umbilical cord blood of mature infant, which was developed to prevent and treat BPD of preterm infant. Its target is preterm infants at high risk for BPD who are in 23~29 weeks of pregnancy, have 500~1,250 g of birth weight, and require continuous therapy with ventilator within 5 ~ 14 days after birth. In clinical trials to identify safety and suitability of the PNEUMOSTEM®, it was stable without any adverse event within 6 hr after therapy. Although significant adverse events occurred in 6 subjects after that, there was no significant difference from the control group. The test group showed significantly lower severity of disease compared with the control group. The 'PNEUMOSTEM®' was assigned as an 'orphan drug' in U.S. and Europe and clinical studies for it are on progress in Korea and U.S.. Accordingly, it is expected that the 'PNEUMOSTEM®' will be introduced into the Korean medical market and utilized for preventing and treating BPD of preterm infants. Provided it is considered that accumulating basis for efficacy and safety of this medicine and understanding its cost effectiveness will be required.

1. Disease background and disease burden

1.1. Bronchopulmonary dysplasia (BPD)

BPD is a chronic pulmonary disease occurring patients who received ventilation therapy and oxygen therapy from infant respiratory distress syndrome and often developed in preterm infants with shorter gestational age and lesser birth weight. It is one of main causes for deaths and complications in preterm infants and developed in about 10~30% of preterm infants with birth weight less than 1,500 g[1]. It is estimated that about 2,400 patients occur in Korea annually. Its mortality rate is higher in infants requiring respiratory therapy for at least 6 months as 10~25%. Although there are some deaths from right heart failure or necrotic bronchiolitis, its prognosis is likely to be good[2].

1.2. Disease burden

As the survival rate of preterm infants increases with development of health technology, it is expected that frequency of BPD will continue to increase[3]. It was found according to statistical health insurance data that the number of patients with BPD in pre and postnatal period in Korea in 2014 was 784 and annual medical cost for them was estimated as 3.52 billion won (Table 1)[4].

〈Table 1〉 Bronchopulmonary dysplasia originated in pre and postnatal period in Korea.

(Unit: persons, thousand won, year)

Classification	2014		2013		2012	
	Patients	Medical cost	Patients	Medical cost	Patients	Medical cost
Inpatient	141	2,742,965	156	2,377,192	202	2,267,671
Outpatient	709	778,211	909	830,839	747	796,469
Total	784	3,521,176	992	3,208,030	870	3,064,141

*Source: Statistics on disease practice by Health Insurance Research & Assessment (http://www.hira.or.kr/)

2. Detailed description of health technology

'Drug for BPD in preterm infants, PNEUMOSTEM®' is a drug produced from mesenchymal stem cells extracted from umbilical cord blood of full term infants (liquid for injection). It is expected able to regenerate pulmonary tissue of preterm infants and improve inflammation[5].

2.1. Precedure

Mix human mesenchymal stem cells (1×107 cells/kg or 2×107 cells/kg) and normal saline (2 ml/kg or 4 ml/kg) for preparation. The prepared injection liquid is sucked into a syringe and half of its total volume is administrated to a patient in lateral decubitus position (left) via a gavage tube. Residual liquid is administrated repeatedly to the patient in lateral decubitus position (right) to transfer it to both sides of the lung. The administration of injection liquid will be taken within 5 min[6].

2.2. Related status

In 2008, allogenic umbilical cord blood derived mesenchymal stem cell drug to regenerate pulmonary cells of patient with chronic pulmonary disease obtained a patent (Application No.: 10-2007-0010191). The PNEUMOSTEM® was assigned as an 'orphan drug at developmental phase'. It secured a right for exclusive sales of drug for BPD by being assigned as an 'orphan drug' from U.S. Food and Drug Administraion and European Medicine Agency (EMA). Currently, phase II clinical study is on progress in Samsung Seoul Hospital and Seoul Asan Hospital and phase I and II clinical trials were started in U.S. from March in this year[5].

3. Alternative therapy and existing similar health technologies

There is no definite preventive or therapeutic method to BPD and only rescue therapies within restricted range are being progressed. In actual clinical conditions, several methods including administration of adrenocortical steroid in pre and postnatal period, artificial ventilation, premature closure of parent ductus arteriosus (PDA), treatment of pre and postnatal infection, limitation of water supply, and nutritional supplement including vitamin A are being used. However there is no strategy with securely proved effectiveness[7].

4. Health technology assessment: safety and effectiveness [7]

- Chang et al. (2014) observed abnormal responses and disease severity to understand safety and adequacy of the drug in dose-escalation trial subject to total 9 patients in 1 medical center.
- The study was performed against preterm infants at high risk of BPD with 500~1,250 g of birth weight in 23~29 weeks of pregnancy and compared with the control group with similar severity in the same ventilation conditions. To initial 3 patients, lose dose (1×107 cells/kg) was administered and then high dose (2×107 cells/kg) was given to 6 patients later.

4.1. Safety

- There was no adverse event or damage of respiratory system and cardiovascular system within 6 hr after treatment and all of them survived and were discharged.
- Then significant adverse events were developed in 6 patients, but there was no significant difference from the control group; PDA ligation (4 patients), pneumothorax (1patient), periventricular leukomalacia (1 patient). The test group showed significantly lower severity of disease compared with the control group.

4.2. Effectiveness

- Althoug the test group showed a trend of decreasing respiratory severity score in comparison with the control group 3 days after treatment, there was no significant difference.
- The cytokine value (MMP-9, IL-6, IL-8, TNF-α, TGF-β) of airway aspirate was significantly low on the 7th day after treatment.

5. Domestic and foreign cost related information

Although accurate information on the cost of this product cannot be determined, it is generally known as about 5~7 million won per 1 vial in case of stem cell related therapeutic agent in current medical market.

6. Current study in progress

As results reviewing related information via Database on Clinical Trials (https://clinicaltrials.gov), it was identified that there were total 6 studies (as of July, 2015), wherein 1 study was completed and 6 studies were in progress.

〈Table 2〉 Clinical studies related to bronchopulmonary dysplasia in preterm infants[8), 9)].

Phase	ID	Title of study	Subjects (No.)	Target condition	Intervention	Result parameters	Status
Phase I	NCT1297205	Safety and efficacy evaluation of PNEUMOSTEM® treatment in Premature infants with BPD	9	Preterm infants at high risk of BPD	PNEUMOSTEM®	Adverse drug response (12 weeks from the day of treatment)	Completed
Follow-up	NCT01632475	Follow-up study of safety and efficacy of PNEUMOSTEM® in premature infants with BPD				Drug related adverse events, Blood test, chest x-ray, physical examination	In progress
Follow-up	NCT02023788	Long-term safety and efficacy follow-up study of PNEUMOSTEM® in patients who completed PNEUMOSTEM® Phase I study				Drug related adverse events, Blood test, chest x-ray, physical examination	In progress
Phase II	NCT01828957	Efficacy and safety evaluation of PNEUMOSTEM® versus a control group for treatment of BPD in premature infants	70	Preterm infants at high risk of BPD	PNEUMOSTEM® vs Normal saline	Prevalence of BPD (moderate to severe) or mortality at 36 weeks PMA)	In progress
Follow-up	NCT01897987	Follow-up safety and efficacy evaluation on subjects who completed PNEUMOSTEM® Phase II clinical trial				Respiratory outcome: readmission rate and duration of the hospital stay due to respiratory infection	In progress
Phase II	NCT02381366	Safety and efficacy of two Dose Levels of PNEUMOSTEM® in preamature infants at High risk for BPD - a U.S. study	12	Preterm infants at high risk of BPD	PNEUMOSTEM®	Adverse drug response (84 days after treatment)	In progress

BPD, bronchopulmonary dysplasia; PMA, post-menstrual age

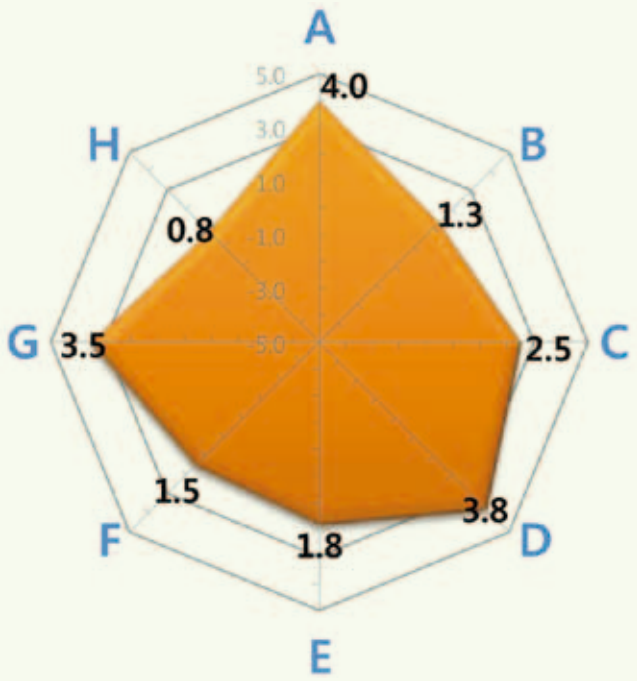
7. Social impact through expert's advice

These are opinion of 4 experts in the relevant clinical department selected randomly in the pool of National Evidence- based Collaborate Agency (NECA) comprising 800 health technology assessment experts.

It is expected that the 'PNEUMOSTEM®', a drug for BPD in preterm infants will be a therapeutic alternative to patients having no treatment. It is considered that it can decrease potential disease progression from chronicization and contribute to reduce prevalence of various complications. It is also considered that its medical treatment is not difficult and has little risk during therapy.

But this expectation to stem cell drug may be excessive because of deficient clinical background. Especially it is considered that long term assessment of effectiveness and complications would be required further and the safety for extrinsic biological agent should be validated definitely. In addition review on the cost effectiveness is necessary also.

Accordingly, these experts discussed, resulting that although clinical bases to date were deficient, it would be a positive therapy model as a drug for preterm infant BPD and accumulation of backgrounds and verification of cost-effectiveness would be needed through large scale randomized control trial study in future.



A. Fulfillment of unmet needs; B. Improvement in patients' health; C. Impact on health disparities; D. Impact on health disparities; E. Acceptability to patients; F. Acceptability to clinicians; G. Changes in healthcare costs; H. Social, Ethical and legal impact

※ This graph presents mean values of results on positive or negative potential impact of PNEUMOSTEM® assessment by medical professionals with ±1~5 points of scale.

〈Figure 1〉 The result of scoring potential impacts of 'PNEUMOSTEM®'.

References

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This report was prepared for the purpose of providing objective information on domestic and foreign promising health technology under development. Contents of this report were referenced from research literature and health technology assessment report related to this technology and included study results obtained from expert advices of the medical field.

It was declared that the National Evidence based Healthcare Collaborating Agency and the authors have no interest with any specific company.

NECA National Evidence-based Healthcare Collaborating Agency

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