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A first-in-human, open-label, dose-escalation study to investigate the safety and tolerability of CHC2014, a tropomyosin receptor kinase (TRK) inhibitor, in adult patients with advanced solid tumors

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Background

- TRK inhibitors are used to treat adult and pediatric patients with solid tumors based on the presence of a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion[1]. CHC2014 (= NOV1601), a highly selective pan-TRK inhibitor, shows anti-tumor activity against tumors harboring wild-type or solvent front mutated *NTRK* fusions in non-clinical studies. This is the first-in-human dose-escalation study of oral pan-TRK inhibitor, CHC2014, in subjects with advanced solid tumors.

Non-clinical study results

- CHC2014 is a novel small molecule of oral route of administration, with unique dynamic configuration to solvent-front mutations of TRK proteins. CHC2014 showed potent and selective growth inhibitory activity against tumor cells harboring wild-type or solvent front mutated *NTRK* fusions (Figure 1, Table 1, and Figure 2).
- CHC2014 showed potent in vitro and in vivo anti-tumor activities against tumors harboring *NTRK* fusion. To evaluate PK profiles of CHC2014 in plasma and tumor from subcutaneous KM-12 xenograft BABL/C-nu/nu mouse model, these mice were treated with CHC2014 daily administered for 14 days. The AUC of tumor was 22-fold of the AUC of plasma. The tumor concentrations appeared to be higher than plasma concentrations at day 14 (Figure 3).

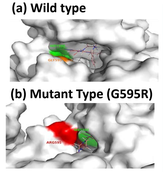

Figure 1. ***In silico*** **molecular docking of CH2014 on wild and solvent front mutated TRKA (G595R)**

Cell line	*NTRK* rearrangement	IC_{50} (nM) NOV1601	IC_{50} (nM) LOXO-101
KM-12	*TPM3-NTRK1*	7.3	10.4
NIH3T3-MPRIP-NTRK1	*MPRIP-NTRK1*	5.4	2.5
NIH3T3-ETV6-NTRK3	*ETV6-NTRK3*	37.9	19.1
Ba/F3-LMNA-NTRK1	*LMNA-NTRK1*	21	11
Ba/F3-ETV6-NTRK2	*ETV6-NTRK2*	24	18
Ba/F3-ETV6-NTRK3	*ETV6-NTRK3*	29	13
Ba/F3-LMNA-NTRK1 (G595R)	*LMNA-NTRK1* (G595R)	45	3,749
Ba/F3-ETV6-NTRK3 (G623R)	*ETV6-NTRK3* (G623R)	28	1,005
NIH3T3	-	>10,000	>10,000
Ba/F3 (+ mIL-3)	-	>10,000	>10,000

Table 1. Inhibition of cell proliferation in various cell lines harboring *NTRK* rearrangements (wild type and resistant mutations)

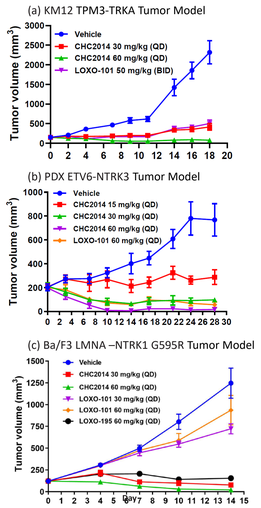

Figure 2. In vivo efficacy of CHC2014

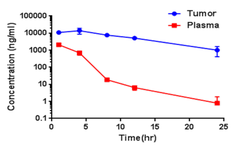

Figure 3. Tumor-to-plasma exposure ratio of CHC2014 in KM-12 xenograft mouse model

Methods

- This phase 1, open-label, multi-center, dose-escalation study at 4 centers in Korea (NCT04014257) enrolled 17 subjects into 5 dose-escalation cohorts; doses ranged from 50 to 300 mg given once a day (QD).
- The primary objective was to determine the recommended phase 2 dose (RP2D) or maximum tolerated dose (MTD). The secondary objectives were to determine the pharmacokinetic (PK) characteristics and assess safety and tolerability.

Results

- Ten male and seven female subjects aged between 28-73 years received treatment with CHC2014 (6 non-small cell lung cancers, 4 head and neck cancers, 2 uterine cancers, and 1 each of glioblastoma, pancreatic, bile duct, prostate, and ovarian cancer).
- There were no dose-limiting toxicities at 5 dose levels and MTD was not reached.
- The systemic exposure was dose-proportional from 50 to 300 mg with once-daily multiple administrations.
- The most frequently reported treatment-related treatment-emergent adverse events (TEAEs) were fatigue (23.5%), dysgeusia, constipation, and dyspepsia (each 17.6%), which were mostly Grade 1 or 2. Only one case of Grade 3 anemia was reported in the 300 mg QD cohort. There was no subject with treatment-related serious TEAE.
- Six subjects had stable disease based on RECIST 1.1 and RANO criteria.

Table 2: Baseline characteristics

	50 mg QD (N = 3)	100 mg QD (N = 4)	150 mg QD (N = 4)	200 mg QD (N = 3)	300 mg QD (N = 3)	Total (N = 17)
Age (Years)						
Median (Min, Max)	56 (47, 64)	50 (38, 63)	58 (55, 64)	47 (28, 57)	66 (61, 73)	56 (28, 73)
Sex, n (%)						
Male	2 (66.7)	3 (75.0)	1 (25.0)	2 (66.7)	2 (66.7)	10 (58.8)
Female	1 (33.3)	1 (25.0)	3 (75.0)	1 (33.3)	1 (33.3)	7 (41.2)
ECOG Performance Status, n (%)						
0	2 (66.7)	2 (50.0)	0	1 (33.3)	0	5 (29.4)
1	1 (33.3)	2 (50.0)	4 (100.0)	1 (33.3)	3 (100.0)	11 (64.7)
2	0	0	0	1 (33.3)	0	1 (5.9)
Tumor Type, n (%)						
Head and Neck	0	0	0	1 (33.3)	3 (100.0)	4 (23.5)
Non Small Cell Lung	2 (66.7)	2 (50.0)	1 (25.0)	1 (33.3)	0	6 (35.3)
Pancreas	1 (33.3)	0	0	0	0	1 (5.9)
Bile Duct	0	1 (25.0)	0	0	0	1 (5.9)
Prostate	0	0	1 (25.0)	0	0	1 (5.9)
Ovary	0	0	1 (25.0)	0	0	1 (5.9)
Uterus (Body)	0	1 (25.0)	1 (25.0)	0	0	2 (11.8)
Other	0	0	0	1 (33.3)	0	1 (5.9)

Table 3: Treatment-related adverse events

	50 mg QD (N = 3) n (%)	100 mg QD (N = 4) n (%)	150 mg QD (N = 4) n (%)	200 mg QD (N = 3) n (%)	300 mg QD (N = 3) n (%)	Total (N = 17) n (%)
Subjects with at least one treatment-related TEAE	1 (33.3)	1 (25.0)	4 (100.0)	1 (33.3)	2 (66.7)	9 (52.9)
Nervous system disorders	0	0	3 (75.0)	1 (33.3)	1 (33.3)	5 (29.4)
Dysgeusia	0	0	2 (50.0)	0	1 (33.3)	3 (17.6)
Dizziness	0	0	0	1 (33.3)	0	1 (5.9)
Peripheral sensory neuropathy	0	0	1 (25.0)	0	0	1 (5.9)
General disorders and administration site conditions	0	0	2 (50.0)	0	2 (66.7)	4 (23.5)
Fatigue	0	0	2 (50.0)	0	2 (66.7)	4 (23.5)
Gastrointestinal disorders	0	0	2 (50.0)	0	1 (33.3)	3 (17.6)
Constipation	0	0	2 (50.0)	0	1 (33.3)	3 (17.6)
Dyspepsia	0	0	2 (50.0)	0	1 (33.3)	3 (17.6)
Nausea	0	0	1 (25.0)	0	0	1 (5.9)
Investigations	0	1 (25.0)	1 (25.0)	0	1 (33.3)	3 (17.6)
Aspartate aminotransferase increased	0	0	1 (25.0)	0	0	1 (5.9)
Blood fibrinogen increased	0	1 (25.0)	0	0	0	1 (5.9)
Platelet count decreased	0	0	0	0	1 (33.3)	1 (5.9)
Metabolism and nutrition disorders	1 (33.3)	0	1 (25.0)	1 (33.3)	0	3 (17.6)
Decreased appetite	1 (33.3)	0	1 (25.0)	1 (33.3)	0	3 (17.6)
Musculoskeletal and connective tissue disorders	0	0	1 (25.0)	0	2 (66.7)	3 (17.6)
Myalgia	0	0	1 (25.0)	0	2 (66.7)	3 (17.6)
Renal and urinary disorders	1 (33.3)	0	0	0	2 (66.7)	3 (17.6)
Proteinuria	0	0	0	0	2 (66.7)	2 (11.8)
Urinary tract obstruction	1 (33.3)	0	0	0	0	1 (5.9)
Blood and lymphatic system disorders	0	0	1 (25.0)	0	1 (33.3)	2 (11.8)
Anaemia	0	0	1 (25.0)	0	1 (33.3)	2 (11.8)

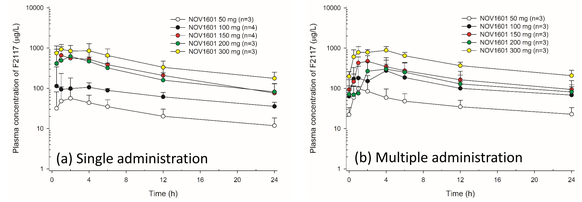

Figure 4. Pharmacokinetic profile of CHC2014

Conclusions

- CHC2014 was safe and well-tolerated at dose levels of 50 to 300 mg QD.
- Doses of 200 and 300 mg QD were defined as RP2D based on PK profile and safety results.
- A multi-national phase 2 study will be conducted to assess the efficacy and safety in patients with *NTRK* fusions.

References

1. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731-747. doi:10.1038/s41571-018-0113-0

Disclosure: Tak Yun declares no competing interests. **Funding:** Handok Inc., CMG Pharmaceutical Co. Ltd., and National OncoVenture (supported by National Cancer Center, designated by the Ministry of Health and Welfare Korea).